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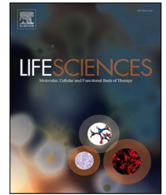

JNK signaling and its impact on neural cell maturation and differentiation

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ABSTRACT

C-Jun-N-terminal-kinases (JNKs), members of the mitogen-activated-protein-kinase family, are significantly linked with neurological and neurodegenerative pathologies and cancer progression. However, JNKs serve key roles under physiological conditions, particularly within the central-nervous-system (CNS), where they are critical in governing neural proliferation and differentiation during both embryogenesis and adult stages. These processes control the development of CNS, avoiding neurodevelopment disorders. JNK are key to maintain the proper activity of neural-stem-cells (NSC) and neural-progenitors (NPC) that exist in adults, which keep the convenient brain plasticity and homeostasis. This review underscores how the interaction of JNK with upstream and downstream molecules acts as a regulatory mechanism to manage the self-renewal capacity and differentiation of NSC/NPC during CNS development and in adult neurogenic niches. Evidence suggests that JNK is reliant on non-canonical Wnt components, Fbw7-ubiquitin-ligase, and WDR62-scaffold-protein, regulating substrates such as transcription factors and cytoskeletal proteins. Therefore, understanding which pathways and

Abbreviations: ABL, Abelson non-receptor tyrosine kinase; ANSC, adult neural stem cell; ANPC, Adult neural progenitor cell; AP-1, Activating protein 1; ATF-2, Activating transcription factor-2; BOC, Biregional cell adhesion molecule-related/down-regulated by oncogenes (Cdon) binding protein; C-JUN, Jun Proto-Oncogene, AP-1 Transcription Factor Subunit; C-FOS, Fos Proto-Oncogene, AP-1 Transcription Factor Subunit; CNS, central nervous system; CREB, Cyclic Adenosine Monophosphate Response Element-Binding Protein; DG, dentate gyrus; EBs, Embryoid bodies; EGF, epidermal growth factor; ERK, extracellular signal-regulated kinase; ESC, embryonic stem cells; Fbw7, F-box and WD repeat domain containing-7; FGF, Fibroblast Growth Factor; IFN-γ, interferon gamma; Fz/FZD, Frizzled; GCL, granular cell layer; GEF, Guanine nucleotide exchange factor; GTPases, guanosine triphosphatases; hESC, human embryonic stem cells; hMSC, human Mesenchymal stem cells; hPSC, human pluripotent stem cell; IL-1β, interleukin 1 beta; JIP, JNK-interacting protein; JNK, Jun N-terminal kinase; Klf4, Krüppel-like factor 4; KO, knockout; LRP6, Low-density lipoprotein receptor related protein; MAP, Microtubule associated protein; MAPK, Mitogen-activated protein kinases; MEF, Murine embryonic fibroblasts; mDA, Midbrain dopaminergic; NGF, Nerve Growth Factor; PCP, Planar Cell Polarity; PSD95, Postsynaptic density protein-95; RA, retinoic acid; Rac 1, Rac Family Small GTPase 1; Shh, Sonic-hedgehog-protein; SFPQ, Splicing factor proline and glutamine rich; SGZ, subgranular zone; STEF, Sif and Tiam1-like exchange factor; STAT, Signal Transducer and Activator of Transcription; Tiam 1, TIAM Rac1 associated GEF 1 (Guanine Exchange Factor); TLR5, Toll-like receptor; TNFα, Tumor necrosis factor; WT, Wild type.

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molecules interact with JNK will bring knowledge on how JNK activation orchestrates neuronal processes that occur in CNS development and brain disorders.

1. Introduction

This review focuses on the mechanisms controlled by JNK signaling involved in brain development and adult neurogenesis. It is organized into several sections. There is information about the general aspects of the JNK pathway, followed by a presentation of experimental findings from *in vitro* cell cultures. These findings highlight the critical role of JNK in regulating cell proliferation, which varies depending on JNK isoforms and the cellular context. Subsequent sections provide a detailed exploration of the interactions between various molecules and pathways within JNK signaling, emphasizing how the cellular context influences the outcome of JNK signaling, whether it leads to differentiation or apoptosis. Additionally, a section discusses studies elucidating JNK signaling's role in neurite and axonal outgrowth. The review concludes with a summary of data showing how JNK, in an isoform-specific manner, regulates adult neurogenesis in mice.

2. General aspect of JNK signaling pathway in central nervous system

C-Jun N-terminal kinases (JNKs), members of the Mitogen-Activated Protein Kinase (MAPK) family, are encoded by three mammalian genes—*Mapk8 (Jnk1), Mapk9 (Jnk2), and Mapk10 (Jnk3)*—resulting in ten distinct isoforms that are differentially distributed throughout the body. JNK1 and JNK2 are expressed ubiquitously, while JNK3 is predominantly found in the heart, testicles, and brain [1,2]. JNKs are activated through phosphorylation by upstream MAPK Kinases (*e.g.*, MKK4/7), which are themselves activated by MAPK Kinase Kinases (MAP3K). Once activated, JNK translocates to the nucleus to modulate the expression of various transcription factors (*e.g.*, ATF-2, c-Jun) and nuclear hormone receptors (Fig. 1) [1,3,5,6]. Additionally, JNK can phosphorylate transmembrane receptors and cytosolic substrates, such as cytoskeletal-associated proteins, vesicular transporters, and JNK-interacting proteins (JIP1/JIP3) [1,5,6]. This substrate diversity partly explains why JNKs are implicated in a wide range of cellular functions [1]. Under physiological conditions, the JNK pathway plays significant roles, including the development of the CNS, specifically in controlling neural stem cell (NSC) proliferation and differentiation, as well as in directing cortical neuronal migration to specific layers where synaptic contacts are formed [7,8]. Conversely, the JNK pathway is associated with pathological conditions such as neurodegenerative disorders, inflammation, and plays crucial roles in cancer progression, particularly through its links to immune evasion, compensatory cell proliferation, and autophagic control [9–11]. In summary, there is substantial evidence indicating that the JNK pathway regulates both cell apoptosis and cell survival [2,12].

2.1. The regulatory role of scaffolding proteins in JNK neural activity

JNK-interacting proteins (JIPs) are scaffolding proteins that enhance the localization and modulation of JNKs in response to distinct stimuli [13–15]. JIPs selectively recruit specific JNK isoforms, their upstream kinases like MKK7 and Dual Leucine Zipper Kinase (DLK), as well as associated phosphatases (Fig. 1) [16–18], and facilitate the recruitment of Ras Homolog Gene Family, Member A (Rho A), and other GTPase family members [19]. Notably, JNK/Stress-Activated Protein Kinase-associated protein 1 (JIP3/JSAP1) shows a higher binding affinity for JNK3 than for JNK1 and JNK2, directing signaling modules such as MEKK1-MKK4-JNKs, MLK3-MKK7-JNKs, and ASK1-MKK4/7-JNKs [20]. JIP3/JSAP1-null embryonic stem cell (ESC) lines exhibit alterations in multiple components of JNK signaling, leading to differentiation defects in the early formation of embryonic bodies (EB). Crucially, the JIP3/JNK3 interaction is essential for neuroectoderm formation during early embryogenesis, as both proteins are co-expressed in neuroectodermal β-tubulin III-positive cells at the E7.5 embryonic stage. Moreover, the absence of neuronal JIP3/JSAP1 affects proper neurite outgrowth and induces alterations in axonal transport [21]. JIP3/JNK3 is also a target for retinoic acid (RA) stimulation of differentiation in ESCs [21,22].

Experimental evidence from *Jip3*$^{-/-}$ and *Jip1*$^{-/-}$ mice consistently highlights developmental abnormalities, including axon shortening in the commissural tract of the telencephalon [23,24]. Specifically, JIP1 orchestrates JNK activation by arranging the MLK-MKK7-JNK signaling module, which negatively regulates *N*-methyl-D-aspartate receptor (NMDAR)-dependent synaptic plasticity and memory [25]. Biochemical and microscopy methods have demonstrated that JIP1 interacts with JNK3 and Postsynaptic density protein-95 (PSD95) in the spines of hippocampal neurons, suggesting its role in shaping dendritic spine morphology (Fig. 1) [26]. Furthermore, the loss of another JIP isoform, JIP2, correlates with downregulation of JNK proteins and impairs the generation of mature neurons, as observed in rare genetic disorders such as Phelan-McDermid syndrome [27].

3. JNK signaling regulates cell proliferation in a context dependent manner

The role of JNK/c-Jun signaling in cell cycle regulation is not well understood. Experiments with JNK knockout (KO) mice have revealed the significant impact of the JNK signaling pathway on self-renewal and differentiation, critical features in various stem cell types including embryonic, induced pluripotent, and adult tissue-specific stem cells. A gain-of-function model in Murine Embryonic Fibroblasts (MEFs) lacking JNK1 and JNK2 (*Jnk1/2*$^{-/-}$) was created by inducing JNK1 and JNK2 expression. This model identified an inverse correlation between JNK-cJun signaling and the cytoplasmic substrate Stathmin (STMN), also known as Oncoprotein 18 (Op18), which is prevalent in proliferative cells. This interaction was further supported by shRNA-mediated downregulation of STMN in *Jnk1/2*$^{-/-}$ null MEFs, offering new insights into JNK's role as a cell cycle regulator [28,29].

Further studies using MEF knock-down for specific JNK isoforms demonstrated that the relationship between JNK/c-Jun signaling and cell proliferation is isoform-specific. While *Jnk1*$^{-/-}$ and *Jnk1*$^{-/-}$ *Jnk2*$^{-/-}$ MEF cultures exhibited slower proliferation compared to wild-type (WT) MEF cells, *Jnk2*$^{-/-}$ MEFs proliferated more rapidly than WT MEFs. These contrasting phenotypes underscore the compensatory gain-of-function of the remaining JNK isoform. In cases where JNK2 was absent, JNK1 activity was enhanced, indicating that JNK signaling is crucial for proper proliferation control, with JNK1 playing a more significant role than JNK2. Additionally, proliferation defects in MEFs lacking or with mutated c-Jun protein suggest that JNK signaling controls proliferation through c-Jun phosphorylation. However, this signaling is not essential for embryonic stem cell (ESC) proliferation [29,30]. In ESCs, JNK influences cell cycle progression in a context-specific manner, as evidenced by the similar proliferation rates in WT and *Jnk1*$^{-/-}$ ESCs, and increased rates in *Jnk2*$^{-/-}$ ESCs and double mutant *Jnk1*$^{-/-}$*Jnk2*$^{-/-}$ ESCs compared to WT cells [20]. These findings suggest that in ESC cultures, JNK affects cell cycle progression in a context-specific manner, rather than being crucial for cell cycle regulation. ESCs obtained from double mutant mice lacking both *Jnk1* and *Jnk2* (*Jnk1*$^{-/-}$*Jnk2*$^{-/-}$) grew faster than WT ESCs when cultured as undifferentiated colonies on feeder layers of inactivated MEF. Conversely, they exhibited a proliferation defect when cultured as Embryoid bodies (EBs). These results suggest that the effect of JNK control on proliferation depends on the cellular context, whether

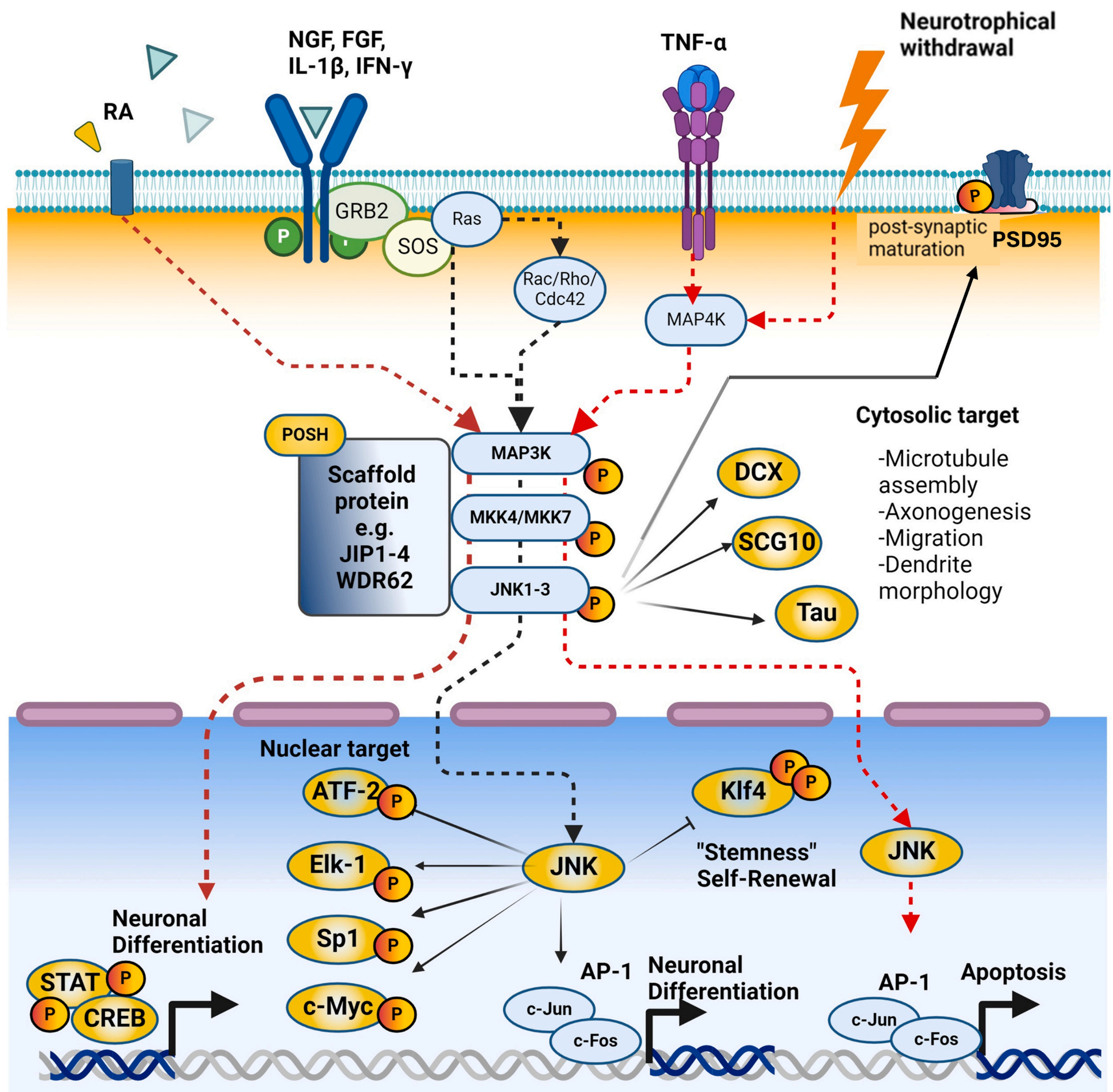

Fig. 1. Schematic Overview of the JNK Signaling Pathway in neurons. The diagram illustrates the activation of the JNK pathway by extracellular ligands *via* plasma membrane receptors such as FGFR, NGFR, IFNAR, and TLR. This activation process involves a sequential phosphorylation cascade of protein kinases (MAP3K, MKK4/7, JNK), which is facilitated by JIPs and WDR62 scaffolding proteins. JNK then phosphorylates cytosolic proteins like DCX, Tau, and SCG10, which play crucial roles in modulating cytoskeletal dynamics. These activities are integral to controlling various cellular processes, including dendrite outgrowth and axonogenesis. Additionally, JNK phosphorylates transcription factors such as ATF2, c-Jun, c-Fos, Elk1, Sp1, Myc, STAT, CREB, and Klf4. The cellular outcomes—ranging from self-renewal and proliferation to differentiation or apoptosis—depend on contextual factors and external stimuli. The diagram further highlights the differential role of AP-1, a transcription factor complex comprised of Jun and Fos subunits, which orchestrates various processes depending on the signaling context. For example, TNF may induce apoptosis, while growth factors or neurotrophic factors promote neural differentiation. The activation by retinoic acid (RA) of transcription factors like STAT and CREB regulates neuronal differentiation, whereas Klf4 activation influences the balance between stem cell self-renewal and differentiation.
Abbreviations. AP-1: Activator Protein 1. **ATF2**: Activating Transcription Factor 2. **Cdc42**: GTPase Guanosine Triphosphatase. **CREB**: cAMP Response Element-Binding. **c-Jun**: Jun Proto-Oncogene. AP-1 Transcription Factor Subunit. **c-Fos**: Proto-Oncogene, AP-1 Transcription Factor Subunit. **DCX**: Doublecortin. **Elk1**: ETS Like Protein 1. **FGF**: Fibroblast Growth Factor. **GRB2**: Growth Factor Receptor-Bound Protein 2. **IL-1β**: Interleukin-1 beta. **IFN-β**: Interferon-gamma. **JNK**: c-Jun N-terminal kinase. **JIPs**: JNK-Interacting Proteins. **Klf4:** Krüppel-like Factor 4. **MAP3K**: Mitogen-Activated Protein Kinase Kinase Kinase. **MKK4/7**: Mitogen-Activated Protein Kinase Kinase 4/7. **Myc**: Myelocytomatosis Proto-Oncogene. **NGF**: Nerve Growth Factor. **POSH**: plenty of SH3. **PSD95**: Postsynaptic density protein-95. **RA**: Retinoic Acid. **Ras/Rac/Rho**: GTPases Guanosine Triphosphatases. **SCG10**: Superior Cervical Ganglion 10. **SOS**: Son of Sevenless. **Sp1**: Specificity Protein 1. **STAT**: Signal Transducer and Activator of Transcription. Tau: Microtubule-Associated Protein Tau. **TNF**: Tumor Necrosis Factor. **WDR62**: WD Repeat Domain 62. Created with BioRender.com.

resembling epiblast cells in the blastocyst or more determinate cells [20].

Biochemically, JNK/c-Jun signaling has been shown to regulate several cell cycle regulators, including cyclin D1, p53, p21 (cip/waf1), p16, and p19 (ARF), which are essential for maintaining cell proliferation under physiological conditions. Specifically, c-Jun's negative regulation of p53 promotes cell proliferation in ESCs cultured as undifferentiated colonies. However, when these cells are grown in EBs, they initiate a differentiation program, similar to that of MEF cells. These differential responses may depend on how JNK regulates p53, which correlates with the length of the G1/G2 phases in various cell types [20,31,32]. This concept is supported by findings from Antonyak et al., who observed that JNK is highly activated in primary brain tumors treated with epidermal growth factor (EGF), promoting tumor cell survival without enhancing cell growth *per se*. Notably, EGF does not activate JNK in non-tumorigenic cells [33,34].

4. JNK activity controls neuronal differentiation

Comparative gene expression analyses between undifferentiated human embryonic stem cells (hESCs) and their differentiated counterparts revealed that genes associated with the JNK signaling pathway, such as *Map4k1 (Hpk1), Map3k7 (Tak1),* and *Jun (cJun)*, were downregulated during the cell differentiation process. This supports the idea that JNK activation is essential for maintaining the undifferentiated state of cells [32]. Additionally, phosphoproteomic analyses conducted by Brill et al., using mass spectrometry, demonstrated differential phosphorylation of JNK signaling proteins such as CRKLb, MINK1, KIAA1804 (MLK4), and TRAF4 in undifferentiated hESCs compared to differentiated derivatives [32,35]. Genome-scale CRISPR/Cas screens for high-throughput discovery of genes involved in differentiation highlighted *Jnk-Jun* family genes as inhibitors of endoderm differentiation. These genes, along with *Smad2/3 and Oct4/Nanog*, which encode transcription factors, block chromatin accessibility and impede the downregulation of genes necessary for the differentiation process. These results indicate that while the JNK/JUN pathway is not essential for maintaining pluripotency, it inhibits cell differentiation, similar to the effects observed with JNK inhibitors [36].

The use of knockdown JNK culture cells reported more data about JNK isoforms in cell-linage specification control. *In vitro* analyses using murine $Jnk1^{-/-}$ and $Jnk2^{-/-}$ ESC lines showed aberrant development of cardiac and mesodermal cells. Similar results were obtained from *in vivo* studies using ESC-derived teratomas lacking *Jnk1* or *Jnk2*, where the development of mesodermal and ectodermal cells was significantly impaired, but not endodermal cells. This supports the role of JNK isoforms in specific cell differentiation [20]. The differentiation of ESCs into primitive neuroepithelial cells following exposure to Fibroblast Growth Factor (FGF) occurs through the JNK and ERK (extracellular signal-regulated kinase) pathways, with a notable role for JNK1 and ERK2 isoforms, as highlighted by pharmacological and genetic analyses [37]. The crucial role of JNK1 was further confirmed by studies on $Jnk1^{-/-}$ ESC lines subjected to an EB differentiation protocol, which showed no neural differentiation, unlike WT, $Jnk2^{-/-}$, and $Jnk3^{-/-}$ genotypes that revealed an increase in E-cadherin levels—a marker for the epithelial lineage—along with low levels of Wnt-4 and Wnt-6, known inhibitors of ESC neurogenesis [38].

A phosphorylation kinase array revealed that JNK2, in addition to JNK1, plays a role in ESC differentiation control through the phosphorylation of the transcription factor Krüppel-like factor (Klf4), which is highly expressed in the undifferentiated state and decreases rapidly upon differentiation initiation. The phosphorylation of Klf4 at Thr224 and Thr225 by JNK1 and JNK2 reduces its transcriptional and transactivation activities, thereby reducing ESC self-renewal capacity and accelerating differentiation, as well as enhancing somatic cell reprogramming [39].

Various components known to control differentiation processes, such as retinoic acid (RA), nerve growth factor (NGF), and cytokines like interferon gamma (IFN-γ) and interleukin 1 beta (IL-1β), have been found to activate the JNK pathway. Specifically, RA stimulates the JNK pathway by activating transcription factors such as STAT1/2, CREB, and ATF-2, which promote neuronal induction [40–42]. IFN-γ enhances JNK activity, inducing neurite outgrowth and β-III tubulin expression in pheochromocytoma PC12 cells, murine adult NSCs, and C17.2 NPCs [43]. IL-1β, through the Wnt/JNK pathway, contributes to neuronal differentiation of NPCs [44,45].

The role of JNK in differentiation control was also evidenced in proliferating tumoral PC12 cells following NGF stimulation. This neurotrophic factor binds to NTRK1 (neurotrophic tyrosine kinase receptor 1), leading to the activation of downstream signaling cascades such as the Ras/Raf/Erk1–2, PI3K, and JNK pathways, resulting in increased expression of genes involved in sympathetic neuronal differentiation. A quantitative mass-spectrometry-based proteomic method identified various differential kinetic partners that interact with JNK during this differentiation process, including small GTPases (Gα, Ras, Cdc42), actin-binding proteins, microtubule-binding proteins, and RNA-binding proteins [46]. Further analysis showed that JNK1 interacts with RNA-binding proteins SFPQ and NONO, which correlates with the induction of PC12 neuronal differentiation [46]. Additionally, the transfection of JNK3-p54 in PC12 cells, which typically express only JNK1 and JNK2, led to an increase in the number and length of neurites after NGF stimulation, mediated through c-Jun phosphorylation. This highlights JNK3's role in differentiation, despite its association with apoptosis induction in oligodendrocytes treated with NGF. Since in both type of cell, the NGF stimulation resulted in JNK3 activation with p75 and Rac as upstream intermediates, the differential response must be mediated either by downstream molecules of Rac or by modulation of the p75 tyrosine receptor kinase A interaction. This supports the notion that JNKs, including JNK3, exhibit differential physiological functions depending on the cellular context and the nuclear substrates activated in response to stimuli [47].

In vivo studies using *in-utero* electroporation techniques revealed that STEF (Sif and Tiam1-like exchange factor) and Tiam1 (TIAM Rac1 associated GEF 1), localized at the nuclear envelope, are involved in nuclear regulation and morphology and in re-orientation during front-rear cell polarization. Moreover, it was detected that the STEF/Tiam1/Rac1/JNK complex is crucial in cortical neuronal migration because it is required for acquiring proper leading process morphology, mainly formed by microtubules [48].

The integration of “omic analyses” (proteomic or metabolic) with single-cell methods throughout the differentiation process can provide new insights into how JNK signaling influences differentiation. For instance, analyzing WT ESCs compared to *JNK* knockdown ESCs could reveal the specific roles of JNK signaling in these cells. However, it is crucial to consider the high phenotypic and functional heterogeneity among ESCs when conducting these analyses. This variability must be accounted for to accurately interpret the impact of JNK modulation on cellular differentiation pathways and to discern the subtle changes that may not be evident in more homogeneous cell populations.

4.1. Wnt/JNK pathway

Cell signaling mediated by Wnts and their cell surface receptors plays a pivotal role in the CNS, both during embryonic development and in adult life, influencing processes such as cell division, differentiation, neuronal polarity, axonal outgrowth, migration, and synaptogenesis. Additionally, these signaling pathways are integral to adult hippocampal neurogenesis, functioning in both healthy and diseased states [49,50].

Wnt signaling, which is highly conserved across species, involves over 19 different Wnt genes identified in both mouse and human genomes. These genes activate pathways that can be categorized into the canonical Wnt/β-catenin pathway (Fig. 2A) and the non-canonical

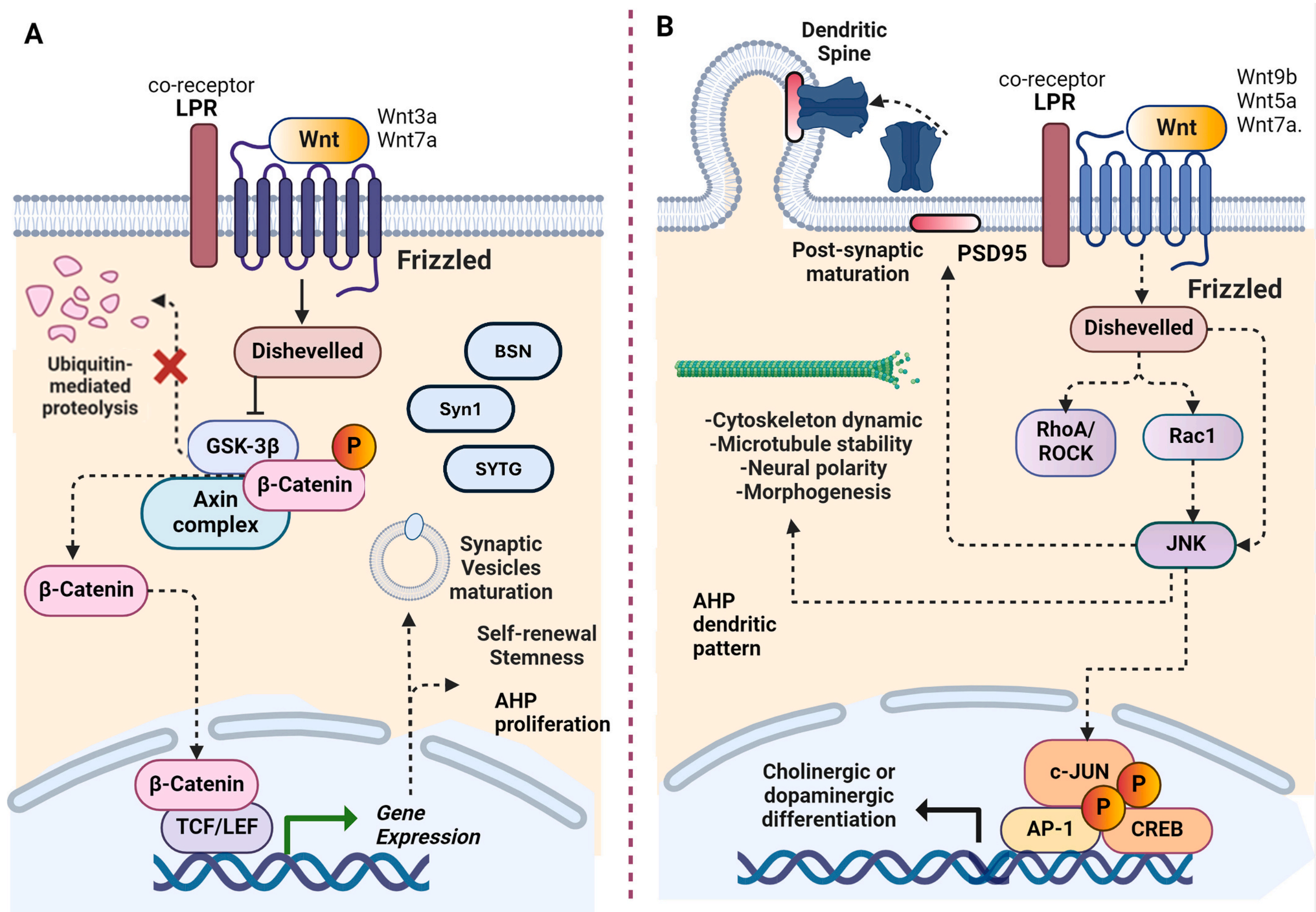

Fig. 2. Schematic representation of neurons illustrating components of the Wnt pathway. (A) The activation of the canonical Wnt/β-catenin pathway leads to the stabilization of β-catenin, which translocates to the nucleus, forming complexes with the transcription factors TCF and LEF, thereby inducing expression of genes that are crucial in regulating stemness self-renewal, synaptic maturation, and AHP. (B) The non-canonical Wnt pathway triggers the activation of the Rho GTPase family proteins (RhoA, ROCK, and RAC1). This cascade further activates the JNK pathway. The Wnt/JNK axis, through cytosolic proteins, plays a pivotal role in regulating microtubule stability, neural polarity, and morphogenesis. It also influences neuronal lineage fate determination through AP-1 and CREB transcription factors. **Abbreviations. AHP: Adult hippocampal proegenitors**. **AP-1**: Activator Protein 1. **CREB**: cAMP Response Element-Binding. **GSK-3β**: Glycogen synthase kinase-3 beta. **JNK**: c-Jun N-terminal kinase. **LEFs**: Lymphoid Enhancer Factor. **PSD95**: Postsynaptic density protein 95. **RAC1**: Rac Family Small GTPase 1 (Guanosine Triphosphatases). **ROCK**: Rho-Associated Protein Kinase. **RhoA**: Ras Homolog Family Member A. **TCF**: T-cell factor **Syn1:** Synapsin-1, **BSN:** Bassoon, **SYTG:** Synaptotagmin. Created with BioRender.com.

pathways, which include the calcium-dependent Wnt/CaMKII and the Wnt/Planar Cell Polarity (PCP) pathways (Fig. 2B). These pathways play crucial roles at various stages of embryonic development, particularly in the maintenance and differentiation of stem cells [51–54].

Wnt-3a, typically a canonical Wnt member, is known to promote early human ESCs differentiation by activating JNK/ATF-2 signaling and neural stem cell (NSC) differentiation through the non-canonical Wnt/AP-1 signaling [55]. Additionally, non-canonical Wnt signaling pathways support the trans-differentiation of human mesenchymal stem cells (hMSCs) into neuro-ectodermal lineages. Specifically, the Wnt-7a/β-catenin pathway, through the FZD5 receptor, induces neuronal differentiation in hMSCs by enhancing neurogenesis and promoting the expression of genes coding for synaptic proteins such as SYN1 (Synapsin-1), BSN (Bassoon), and SYTG (Synaptotagmin) (Fig. 2A). Furthermore, the role of the Wnt/JNK pathway in neuronal differentiation is highlighted by hrWnt-7a, which activates the FZD9 receptor, triggering the differentiation of cholinergic and dopaminergic neurons (Fig. 2B) [56].

In studies involving adult rat hippocampal slices, the Wnt-5a/JNK pathway has been observed to regulate the postsynaptic region by recruiting PSD95 from the cytoplasm to form clusters in dendritic spines, indicating its role in synaptic plasticity and memory formation (Fig. 2B) [51]. The findings by Bengoa-Vergniory et al. support that both Wnt-7a and Wnt-5a activate non-canonical signaling in neurons, driving neuronal differentiation through the involvement of JNK and AP-1 family members [55].

These observations underscore the significance of the Wnt/JNK pathway in neuronal differentiation throughout embryogenesis and into adulthood. Furthermore, genetic studies by Amura et al. on ESCs deficient in JNK isoforms (*Jnk1*$^{-/-}$, *Jnk2*$^{-/-}$, *and Jnk3*$^{-/-}$) have highlighted a critical role for JNK1 in inhibiting the Wnt pathway, as previously described [38].

4.2. Fbw7 protein and SCF-complex pathway

F-box and WD repeat domain-containing 7 (Fbw7) is a component of the SCF (SKP1, CUL1, F-box protein) type E3 ubiquitin ligase complex that plays a crucial role in regulating proteins essential for the viability and differentiation of NSCs and NPCs. The inactivation of Fbw7 in conditional knockout mice has been shown to impair NSC/NPC differentiation, leading to an increase in immature cells and the death of progenitor cells [57]. These effects are accompanied by the accumulation of the transmembrane protein Notch-1 and c-Jun (Fig. 3). Further

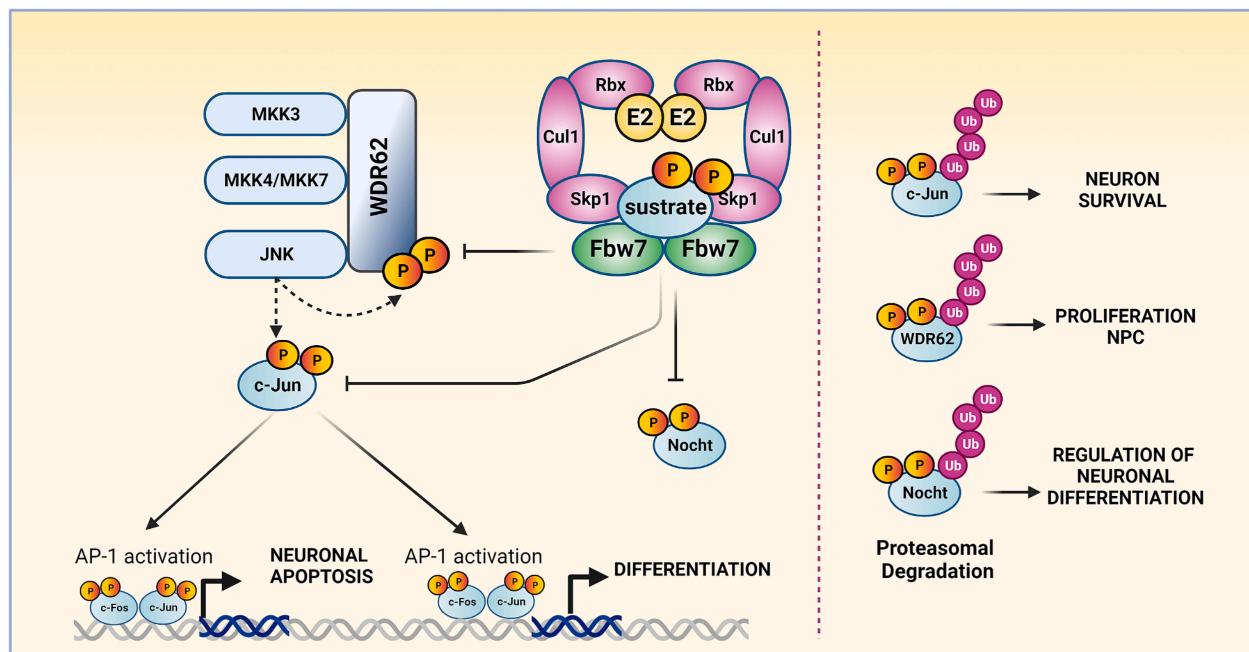

Fig. 3. Intracellular pathways in neural progenitor cells. This illustration depicts the critical role of Fbw7 ubiquitin-ligase in maintaining the stability of the JNK signaling pathway. Fbw7 controls the levels of different phosphorylated substrates (WDR62, c-Jun, and Notch) mediating its ubiquitination and subsequent proteasomal degradation. p-WDR62 requires degradation to initiate proliferation. The levels of p-c-Jun should be reduced to assure neural survival, since is preventing the accumulation of AP-1 that can potentially trigger cell death. Additionally, AP-1 induces the expression of Notch. Achieving optimal levels of p-c-Jun and p-Notch is crucial for inducing neural differentiation. This intricate interplay between phosphorylated and unphosphorylated molecules finely tunes the balance between apoptosis, survival, and neuronal differentiation within the neuron.
Abbreviations. AP-1: Activator Protein 1. **c-Jun**: Jun Proto-Oncogene, AP-1 Transcription Factor Subunit. **c-Fos**: Proto-Oncogene, AP-1 Transcription Factor Subunit. **Fbw7**: F-box/WD repeat-containing protein 7. **JNK**: c-Jun N-terminal kinase. **WDR62**: WD Repeat Domain 62. Created with BioRender.com. **Cul 1**: cullin 1. **Rbx**: ring box protein. **Skp1:** S phase kinase associated protein 1. Created with BioRender.com.

investigations, including genetic and pharmacological rescue experiments, have identified Fbw7 ubiquitin ligase as a molecular switch that counteracts both Notch and JNK/c-Jun signaling. This antagonistic behavior is critical for enabling NSC differentiation and progenitor cell survival. It was also observed that the downregulation of c-Jun could rescue the formation of neurospheres and decrease cell death, both *in vitro* and *in vivo* [57]. Therefore, Fbw7 plays a vital role in controlling neuronal differentiation by antagonizing the Notch and JNK/c-Jun signaling pathways (Fig. 3).

4.3. Cellular context regulates differentiation

JNK signaling is commonly linked to programmed cell death across various systems, including neurons, in response to triggers such as Tumor Necrosis Factor (TNFα) and neurotrophic withdrawal [58,59]. However, the cellular mechanisms underlying this association are not fully understood, as sustained activation of JNK and increased levels of c-Jun are not always necessary to induce neuronal apoptosis. Additionally, merely suppressing JNK or introducing survival factors may not prevent apoptosis, suggesting that other components are necessary to trigger cell death [60]. The role of c-Jun in mediating cellular responses is complex and influenced by numerous factors, including its expression levels, dimerization partners, and interactions with other transcription factors, co-activators, and co-repressors. This multifaceted involvement explains why c-Jun participates in various cellular processes beyond apoptosis, such as proliferation, survival, tumorigenesis, tissue morphogenesis, and axonal regeneration following CNS injury [60,61]. Despite the diversity of the JNK/c-Jun pathway, pharmacological and genetic studies have shown that while JNK is critical for the death of cerebellar granular neurons, AP-1 and c-Jun do not play a dominant role in apoptosis [62]. On the contrary, c-Jun phosphorylation is necessary for JNK-induced neurotoxicity (Fig. 3) [63]. The stability of JNK pathway members is crucial in precisely regulating the choice between apoptosis and differentiation in neuronal stem cells. Fbw7, which ubiquitinates phosphorylated c-Jun, plays a significant role in regulating c-Jun stability (Fig. 3). This regulation facilitates the degradation of c-Jun, which is essential for progenitor survival and neural stem cell differentiation, as previously discussed in Section 4.2. The absence of Fbw7 in neurons leads to increased levels of phosphorylated c-Jun, resulting in neuronal apoptosis [64].

4.4. WDR62/JNK signaling

WD40-Repeat protein 62 (WDR62) is a microtubule-associated signaling protein that plays a crucial role in centrosome biogenesis, cell division, and the differentiation of neural progenitors during brain development. Originally identified as a JNK scaffold protein, WDR62 interacts with JNK1, MKK7, and several MAP3Ks. The interaction between WDR62 and JNK is particularly significant in cortical development, where WDR62 influences the proliferation and differentiation of NPCs, including their migration, through the control of JNK signaling (Fig. 3) [8]. WDR62's involvement with JNK signaling extends to the regulation of NSC mitosis. Specifically, WDR62 governs the symmetric and asymmetric division of NPCs *via* JNK1, as demonstrated during mouse oocyte maturation, where the overexpression of JNK1 can rescue the germ cell loss induced by WDR62 inhibition. This interaction highlights the critical role both proteins play in the development of the reproductive system. However, the specific mechanisms by which WDR62 and JNK signaling regulate meiosis remain less understood [8,65].

5. Neurite initiation and axonal outgrowth depend on JNK activation

Numerous studies have emphasized the crucial role of JNK in neurite outgrowth and axonal elongation [7,66,67], particularly in PC12 and neuroblastoma cell cultures. Upon stimulation with growth factors or retinoic acid (RA), neurite outgrowth is concurrently initiated with the activation of the JNK signaling pathway [68–72]. The specific role of JNK in forming neuronal processes was also studied in the MN9D cell line, a model for dopamine neurons, where exposure to RA induced similar effects [73]. In primary hippocampal neurons, a gradient of phosphorylated JNK (p-JNK) is required for axogenesis, although it is not necessary for dendritic development [54]. During neurite extension in N1E-115 neuroblastoma cells, the internal signaling cascade involving Rac1/Cdc42/JNK and the downstream target paxillin, an actin-binding protein, is activated, highlighting the importance of JNK in cytoskeletal regulation for process formation [74]. Moreover, JNK/STAT1/3 signaling has been identified as necessary for axonal development and neurite outgrowth during neuronal differentiation of ESCs. While STAT3 levels decreased during early neuronal differentiation, phosphorylated STAT1 (p-STAT1) increased significantly, correlating with the rise of Growth Associated Protein 43 (GAP-43), Neurofilament, and βIII-tubulin, which are crucial for neurite outgrowth. Synaptophysin, a synaptic protein, was also reported to be induced (Fig. 4) [42].

The differential involvement of JNK isoforms in neuritogenesis and axogenesis has been observed: JNK3 levels were upregulated during the neurite outgrowth and maturation of ESC-derived cortical neuronal cell types, whereas JNK1 and JNK2 levels decreased [42]. Primary spiral ganglion neurons further highlighted the distinct roles of JNK isoforms in promoting neurite outgrowth [75]. The absence of JNK2 or JNK3, but not JNK1, impeded the initial formation of neurites in dorsal root ganglion neurons. In later stages of neurite elongation, JNK1 and JNK2 isoforms were critical, while JNK3 was not, suggesting that the different isoforms may have unique affinities for various cytoskeletal substrates, notably in regulating microtubule-associated proteins such as MAP1B [67].

Additionally, JNK is activated during neurite formation and axon elongation by the Sonic Hedgehog (Shh) pathway, which plays an essential role in cell differentiation during embryogenesis. The primary receptors for Shh family proteins are the transmembrane glycoproteins C-don (Cell-adhesion-molecule-related/Downregulated by Oncogene) and BOC (Biregional C-don binding protein). Shh/BOC signaling has been associated with microtubule regulation during neurite formation and axon elongation through its interaction with ABL (Abelson's non-receptor tyrosine kinase), leading to subsequent JNK activation. ABL may also interact with and phosphorylate JIP, potentially activating JNK to promote axon formation and outgrowth under growth factor stimuli [76]. This pathway was similarly activated in HEK293T cells, evidenced by an increase in JNK activation during differentiation, concurrent with a rise in BOC and ABL proteins. Specifically, in the PC19 embryonic cell line, it was noted that BOC was activated by interacting with ABL through its putative SH2 binding domain *via* its YXXP motif, which was necessary for inducing JNK activation (Fig. 4).

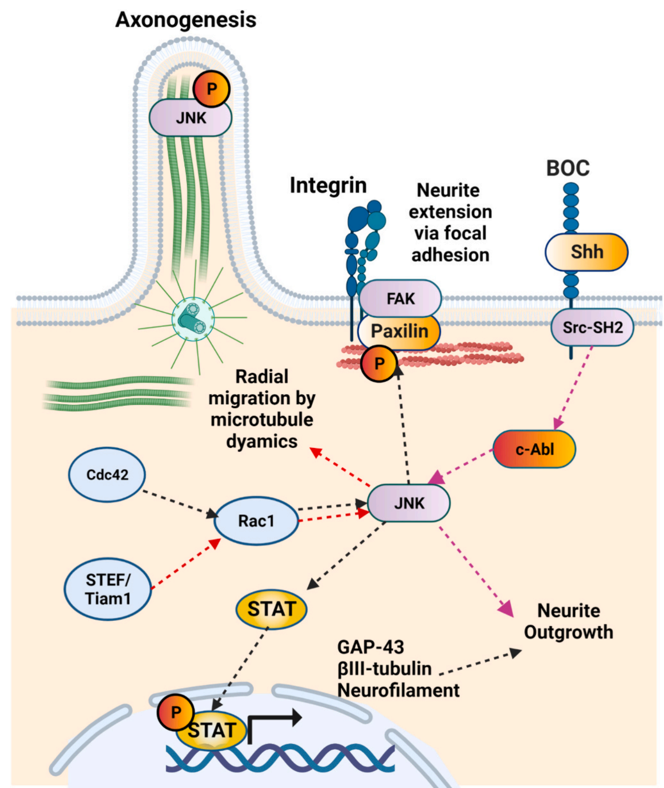

Fig. 4. Schematic pathways that highlight the pivotal role of JNK signaling in axonogenesis, neurite extension, migration, and differentiation. Cdc42, Rac1, and Tiam are proteins activated by different stimuli and regulate the JNK pathway, which, through different cytosolic substrates, controls microtubule dynamics and radial migration, collectively governing axon formation. Notably, JNK-mediated phosphorylation of paxillin driving neurite extension *via* focal adhesion. JNK also intersects with the STAT pathway, specifically under RA induction. The STAT phosphorylation induces the expression of genes (Gap-43, Nefl, and Tubb3) that codify for GAP-43, Neurofilaments and tubulin beta 3, all of them essential for regulating neuronal differentiation. Shh/BOC signaling interacts with Abl, which subsequently activates JNK, controlling microtubule regulation during neurite formation and axon elongation.
Abbreviations. Abl: Abelson non-receptor tyrosine kinase. **BOC**: Brother of Cdo (Cell Adhesion Molecule-Related/Downregulated by Oncogenes). **Cdc42**: Cell Division Control Protein 42 Homolog. **GAP-43**: Growth-Associated Protein 43. **JNK**: c-Jun N-terminal kinase, Nefl: Neurofilament. **RA**: Retinoic Acid. **Rac1**: Rac Family Small GTPase 1 (Guanosine Triphosphatases). **Shh**: Sonic Hedgehog. **STAT**: Signal Transducer and Activator of Transcription. **STEF**: Sif and Tiam1-like exchange factor. **Tiam 1**: TIAM Rac1 associated GEF 1 (Guanine Exchange Factor). Created with BioRender.com.

6. JNK controls adult neural stem cells located in specific mammalian brain regions

In vertebrates such as fishes, amphibians, and reptiles, there is continuous generation of new neurons throughout their lifespan. This regenerative capacity is reduced in birds and is even more limited in mammals, where the generation of new neurons from Adult Neural Stem Cells (ANSCs) is largely confined to two specific brain regions, creating what are considered environmental niches for neurogenesis. One of these regions is the subventricular zone (SVZ), located along the outer walls of the lateral ventricles, and the other is the subgranular zone (SGZ) of the dentate gyrus (DG), positioned at the interface between the hilus and the granular cell layer (GCL) of the hippocampus.

In both the SVZ and SGZ, ANSCs exhibit a glial-like morphology with intermediate filaments such as Nestin and GFAP (glial fibrillary acidic protein), and display a prominent radial process. Under physiological conditions, these ANSCs can either self-renew or give rise to Adult Neural Progenitor Cells (ANPCs) which possess a high proliferation rate and differentiate into neural cells. This leads to the formation of neuroblasts that migrate to specific areas: those from the SVZ integrate into various circuits of the olfactory bulb, playing a crucial role in olfaction, while those from the SGZ move to the granular hippocampal layer, significantly impacting spatial learning and memory, thereby linking this region to behavior and cognition [77–80]. These neurogenic niches host a variety of cell types, including neuroblasts, neurons, astrocytes, and oligodendrocytes, all differentiated from ANSCs, establishing a complex network of intercellular communication. Additionally, microglial cells are present in these areas and differ from those in non-neurogenic niches; they are in contact with various cell types and are

closely associated with the niche vasculature, suggesting an important role in regulating neurogenic activity [81]. The dynamics of these cell interactions, influenced by both intrinsic and external factors, modulate adult neurogenic activity [82–84].

It is important to note that the number of ANSCs located in the SVZ and SGZ decreases significantly with age, unlike other adult cell renewal processes in the body, which proceed at a consistent rate throughout life. Furthermore, there are notable differences in the presence of ANSCs depending on brain size. For example, studies in monkeys (*Callithrix jacchus*) have suggested very low levels of proliferating neuroblasts in the hippocampus during adulthood. This is corroborated by findings in *Macaca mulata* and *Macaca fascicularis*, which show a rate of hippocampal neurogenesis approximately ten times lower than that in adult rodents. In cetaceans, this neurogenic process has not been detected at all [85,86]. These observations indicate that there are distinct rates of adult neuron generation across different mammalian brains, suggesting that findings in rodents cannot be directly applied to other mammals. This has led to numerous studies aiming to understand adult neurogenesis in the human brain, which have resulted in conflicting interpretations [86–88]. Consequently, there is a need to develop new methods to identify and visualize dividing neuronal precursors or to evaluate the age of neurons at the single-cell level [89].

6.1. JNK signal controls adult hippocampal neurogenesis

Research using JNK knockout mice has emphasized that JNK controls adult hippocampal neurogenesis in an isoform-specific manner. Specifically, the absence of JNK1 leads to an increase in immature neurons in the SGZ and a delay in their migration to the granular cell layer [77]. These findings support previous research by Mohammad et al., who demonstrated the role of JNK1 in regulating hippocampal neurogenesis [90]. Furthermore, the use of a double conditional knockout mouse model, which allowed the suppression of *Mkk4* and *Mkk7* genes in the whole organism, confirmed the involvement of the JNK pathway in ANSC control. In the brains of these mice, the reduction of MKK4/MKK7 proteins led to misalignment of immature hippocampal neurons and alterations in their dendritic pattern and maturation [90].

Toll-like receptors (TLRs), particularly TLRs 2, 3, and 4, exhibit distinct effects on various aspects of neurogenesis throughout brain development. Moreover, TLR5, which is expressed in immature cells of the SGZ, inhibits ANSC proliferation through cell cycle regulation and facilitates ANSC neural differentiation *via* the JNK pathway [92].

Intrinsic factors, such as cytokines and glucocorticoids, play a critical role in regulating ANSC activity. The proliferation and activation of astrocytes following acute brain injury, such as cerebral ischemia, intracerebral hemorrhage, or traumatic brain damage are linked to an increase in ANSC/ANPC proliferation and migration towards the damaged area, a mechanism thought to aid brain repair [93]. Specifically, the pro-inflammatory cytokine HMGB1 (High-mobility group box 1), secreted by reactive astrocytes, promotes this ANSC/ANPC proliferation through the activation of the RAGE-dependent JNK signaling pathway (Receptor for Advanced Glycation End products). Thus, the HMGB1/RAGE/JNK pathway might be a promising target to enhance the interaction between astrocytes and ANSCs/ANPCs in the hippocampal neurogenic niche [94].

The activation of microglia, as occurs in various neurodegenerative disorders, decreases the proliferation and survival rate of ANSCs, affecting the adult neurogenesis process. MAPK-signaling pathways, such as p38, JNK, and ERK1/2, play a key role in the pathogenesis of microglia-mediated neuroinflammation. Specifically, the inhibition of JNK signaling and NF-κB in activated microglia by an arginyl-diosgenin analog promotes an increase in the proliferation of ANSCs/ANPCs, as well as the survival of newly generated cells, highlighting the role of JNK in adult neurogenesis control [95].

6.2. JNK through Wnt controls adult hippocampal neurogenesis

Different data support the role of the Wnt/β-catenin pathway in the hippocampal neurogenic niche. *In situ* hybridization revealed the presence of Wnt-3 near the SGZ, and β-galactosidase staining in BATGAL transgenic mice, a reporter strain that expresses β-galactosidase in the presence of activated β-catenin, showed activity of the Wnt/β-catenin pathway in the SGZ and GCL of the DG. Moreover, Wnt-3 is present in adult hippocampal astrocytes, and receptors for components of the Wnt/β-catenin signaling pathway are found in ANPCs. This suggests that Wnt factors secreted by astrocytes could activate the Wnt signaling pathway in ANPCs, controlling their activity, as evidenced by co-cultures between these two cell types. Specifically, the overexpression of Wnt-3, induced by intracellular lentivirus injection in cultured ANPCs, increased neuronal determination and raised neuroblast proliferation. Furthermore, *Wnt7a* knockout mice exhibited a reduction in adult hippocampal neuroprogenitors and an impairment in neuronal differentiation. In contrast, chronic infusion of Wnt7a directly into the rat hippocampus increased the number of immature neurons. Additionally, it was demonstrated that this pathway is necessary for the development of the dendritic pattern of newborn adult hippocampal neurons [96,97]. Using *in vitro* assays on differentiating ANSCs, a transition response from Wnt/β-catenin to Wnt/ PCP signaling was detected. The analyses reported that canonical Wnt-3a/β-catenin promotes ANSC proliferation, while the non-canonical Wnt/PCP/JNK pathway is indispensable for their morphological differentiation. Specifically, Wnt-5a, through the FZD3 receptor, stimulates both JNK and c-Jun [98]. Additionally, Wnt-5a signaling through the CaMKII protein encourages neurogenesis. Both Wnt/JNK and Wnt/CaMKII signaling promote the development of ANPC dendritic morphological patterns [49]. The influence of Wnt signaling on hippocampal neurogenesis is significant because this cellular process is disrupted in neurodegenerative disorders, epilepsy, and stroke. This underlines the importance of the Wnt/JNK pathway as a potential target for developing new strategies against these diseases [55,99].

7. Conclusions

This review has explored the complex roles of the JNK signaling pathway in eliciting specific cellular responses, including neuronal proliferation, differentiation, migration, and even neuronal death, contingent upon the stimulus and cellular context. This signaling pathway engages with various other pathways and signaling molecules, such as Wnt, Shh, GTPases, Fbw7, WDR62, and JIP, impacting the function of final effectors. A significant focus was placed on the AP-1 complex's dual ability to direct cells towards either apoptosis or differentiation, depending on the context. Additionally, the crucial role of the Fbw7 ubiquitin ligase in modulating the phosphorylation levels of c-Jun, thereby influencing the ultimate cellular outcome, was emphasized. It was also noted that in adults, JNK signaling plays a pivotal role in governing neurogenesis, influencing even the final dendritic architecture of newly formed cells. In Table 1 is summarized the role of JNK pathway or each JNK isoform in different *in vitro* and *in vivo* models.

In conclusion, gaining a deeper understanding of how JNK activation influences neuronal processes is crucial for understanding CNS development and brain plasticity in adults. This knowledge holds promising prospects for developing targeted interventions to address abnormal neuronal processes, such as excitability, neural death, or inflammation, which are common in various neurological and neurodegenerative diseases.

Table 1
Summary of *in vitro* and *in vivo* experimental models that reveal the involvement of JNK isoforms in different cellular process.

Stage	Model	Inductor	Assay/phenotype	Effect	Reference
Embryonic stem cells→Neural linage	Cell line 46C Mouse	FGF	SP600125 DN-JNK1a1 DN-JNK2a2	Negative regulation of self-renewal	[37]
Embryonic stem cells→Neural linage	Cell line CCE Mouse	RA	JSAP1-null	Altered Neurite Outgrowth Higher rate of outgrowth Induction of apoptosis	[21]
Embryonic stem cells→Neural linage	Primary cell culture Mouse	RA	JNK1$^{-/-}$	Repression of the Wnt pathway, disruption of neural differentiation	[38]
			JNK2$^{-/-}$	None effect on neural differentiation	
			JNK3$^{-/-}$	None effect on neural differentiation	
Embryonic stem cells→All linages	Primary cell culture Mouse		JNK1$^{-/-}$	JNK-deficient ES cells exhibit abnormal ectodermal development	[20]
			JNK2$^{-/-}$ JNK1$^{-/-}$ JNK2$^{-/-}$	JNK is not essential for ES cell proliferation and self-renewal	
Embryonic Stem Cells→All linages	ES-E14TG2a	LIF withdrawal	SP600125 absence of JNK1 or JNK2	Increases self-renewal Klf4 activation	[39]
Neural Cells Progenitors→Neurons	C17.2 cell line Mouse neonatal Cerebellar derived	PLL	SP600125 IFN-γ	Blocking neurite outgrowth and neuronal Tubulin Beta 3 Class III	[43]
Neural Cell Progenitor	NCP-immortalized Primary from ES Rat	EGF and bFGF	SP600125	Induction of apoptosis and inhibition of proliferation	[100]
PC12 s→ Neural linage	PC12 cell line Rat	NGF	SP600125 D-JNKI-1	Neurite outgrowth JNK interaction with RNA transport granule	[46]
iPSCs→NCPs→Neurons	Human donor	TGF-β inhibitor Noggin dorsomorphin	JIP2 haploinsufficiency 22q13 deletion	Impaired neuronal maturation	[27]
Embryonic stem cells→NCPs→Neurons	P19 Cell Line and BOC$^{-/-}$ E13 cortices	RA Insulin Transferrin Selenite medium	shBOC	Impaired JNK activation during neuronal differentiation. BOC interacts with ABL and activates JNK to promote neurite outgrowth in response to Shh	[76]
Embryonic stem cells Neural Cells Progenitors→Neurons	129Sv and C57Bl/6 Mouse	RA Laminin	SP600125	JNK inhibition in ES cells does not reduced pluripotency or differentiation JNK inhibition is important in the last stage, from neuronal progenitors to neurons abrogates neurogenesis	[101]
Neural Cell Progenitor→Neuron	E16 Embryonic Rat	FGF-2 EGF	L-1β SP600125 IL-1ra	Apoptosis and inhibition of proliferation of NPCs can be reversed by either a SAPK/JNK inhibitor or IL-1ra.	[45]
Embryonic stem cells Neural Cells Progenitors→Neurons	Mouse D3 cell line	RA PLL	SP600125	Activation of JNK is required for neurite outgrowth	[42]
Adult Neuronal Progenitor Cells from hippocampus	Monolayer cell culture 6-week-old Mouse C57/BL6	FGF-2 EGF	JNK inhibitor (JIP-peptide) shRNA Wnt5a	Wnt5a induced morphological development Newborn neurons through the Wnt/JNK and Wnt/CaMKII pathways	[49]
			Wnt5a inhibitor		
Adult Neuronal Progenitor Cells from hippocampus	6-week-old Mouse C57/BL6		Lentivirus Wnt5a shRNA	Wnt5a knockdown impairs the morphological development of adult-born neurons in the hippocampus	[49]
Neural Cells Progenitors→Neurons	9-old-day post-natal Mouse C57BL/6	FGF-2 EGF	Growth hormone (GH) SP600125	Proliferation and survival were significantly decreased under JNK inhibitor	[102]
Adult Neuronal Progenitor Cells From hippocampus	8–16-old-week Mouse C57BL/6		Jnk1$^{-/-}$	JNK1 inhibition lowers anxiety-like behavior and increases adult hippocampal neurogenesis	[90]
			Retrovirus, nuclear JBD	Inhibition of nuclear c-Jun N-terminal kinase (JNK) in adult-born neurons of the hippocampus produces an anxiolytic effect.	
Embryonic stem cells Neural Cells Progenitors→Neuron	D3 cell line and E18 mouse	FGF-2 PLL and Laminin	SP600125	Specific activation of Hes-1promoter by AP-1/JNK signaling Hes-1 is a repressor that maintain neural progenitors by inhibiting neural differentiation	[40]
Embryonic stem cells Neural Cells Progenitors→Neuron	R1 Cell Line	RA LPO and Laminin	SP600125	RA induces ES cell differentiation by activating the MAPK signal transduction pathway. RA-induced CREB activation is mediated by a JNK-dependent mechanism	[41]
Embryonic stem cells NPCs-derived	E14 cortices Rat	bFGF PLO/Fibronectin	siRNA Wnt5a SP600125	Wnt5a-induced neuronal differentiation is regulated by the RhoA/ROCK/JNK pathway.	[44]
Adult Neuronal Progenitor Cells from hippocampus	8-old-week Mouse	Tamoxifen	Mkk4$^{-/-}$/Mkk7$^{-/-}$ Actin-CreETR2	Alterations of dendritic projections of Adult Hippocampal Cells Adult neuroblast migration and differentiation processes alterations	[91]
Adult Neuronal Progenitor Cells from hippocampus	8-old-week Mouse		JNK1$^{-/-}$	Decrease population of early progenitor cells (GFAP$^+$/SOX$^+$), increase of transit amplifying cells population (DCX$^+$)	[77]
			JNK2$^{-/-}$	No changes	
			JNK3$^{-/-}$	Decrease population of early progenitor cells (GFAP$^+$/SOX$^+$)	

(*continued on next page*)

Table 1 (*continued*)

Stage	Model	Inductor	Assay/phenotype	Effect	Reference
Adult Neuronal Progenitor Cells from hippocampus	6- to 7-week-old Primary cell culture	FGF-2 Forskolin RA (LPO)/Laminin	shFZD3	Reduction of JNK and c-Jun phosphorylation/ Activation of JNK by Wnt5a	[98]
Adult Neuronal Progenitor Cells from hippocampus	7-week-old male C57BL/6 Mouse	LPS	Water-soluble arginyl–diosgenin analog (Arg-DG)	Arg-DG inhibits JNK signaling in activated microglia, promoting impaired hippocampal neurogenesis	[95]
Neural Cells Progenitors→Neurons	1–2-day-old neonatal Rat	bFGF	HMGB1 + SP600125	SP600125 blocked activation of JNK signaling induced by by HMGB1	[94]
Adult Neuronal Progenitor Cells→ hippocampu	Primary cell culture Mouse 6-week-old male C57BL/6	EGF bFGF	$TLR5^{-/-}$	The expression of p-JNK was reduced in the neurospheres of the hippocampal DG in the TLR5 KO	[92]
Adult Neuronal Progenitor Cells→ hippocampus	Primary cell culture Mouse 6-week-old male C57BL/6	EGF bFGF	shTLR5 SP600125	The expression of JNK-phosphorylation was reduced by shTLR5-transfected neurospheres The uppression of JNK phosphorilation	[92]

Abbreviations: LPO: Poly-L-Ornithine, bFGF: basic fibroblast growth factor, EGF: Epidemic Growth Factor, LIF: Leukemia Inhibitory Factor, LPS:Lipopolysaccharide. PLL: Poly-D-Lysine, RA: Retinoic acid, TGFβ: Transforming Growth Factor-β, DN: Dominant negative, IFN-γ: Interferon gamma, IL-1β: Interleukin 1 beta, IL-1ra. Interleukin 1 receptor antagonist, JIP: JNK-interacting protein, r JBD: JNK-Binding-Domain, Sh: small hairpin, FZD3: Frizzled Class Receptor 3, TLR: Toll-Like Receptor, HMGB1: high mobility group box 1, AHP: Adult Hippocampal Precursor, CREB: 'cAMP response element-binding', DCX: Doublecortin, SOX: Sex determining Region Y-box 2.

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CRediT authorship contribution statement

Rubén D. Castro-Torres: Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jordi Olloquequi:** Visualization, Data curation. **Jesús Ureña:** Visualization, Supervision. **Miren Ettcheto:** Visualization. **Carlos Beas-Zarate:** Visualization, Project administration, Funding acquisition. **Antoni Camins:** Visualization, Project administration, Funding acquisition. **Ester Verdaguer:** Validation, Supervision, Resources, Methodology, Investigation, Conceptualization. **Carme Auladell:** Writing – review & editing, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare no conflict of interest.

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