

REVIEW ARTICLE

c-Jun: A master regulator of neuroregeneration and neurodegeneration

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Abstract

As a central component of activator protein 1 transcription factors, c-Jun operates through homo- or heterodimerization with the Jun/Fos family members to regulate gene expression. It exhibits dynamic regulation across development, adult homeostasis, and neural injury, establishing c-Jun as a pivotal modulator of diverse neuronal processes. Mounting evidence highlights c-Jun's dual role in neuroprotection and neurodegeneration, influencing neuronal apoptosis, survival, axonal transport, and synaptic plasticity processes closely associated with cognitive decline in neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease. Functional studies using genetic ablation or pharmacological inhibition of c-Jun signaling reveal its biphasic nature: sustained c-Jun activation drives neurodegeneration by inducing pro-apoptotic genes, whereas transient activation promotes neuroregeneration, including axonal sprouting and synaptic remodeling. Phosphorylation of c-Jun at serine 63/73, mediated by its upstream regulator c-Jun N-terminal kinase (JNK), is a key post-translational modification controlling its transcriptional activity. The JNK–c-Jun axis acts as a molecular switch, integrating stress signals to dictate neuronal fate. In neurodegenerative contexts, pathway hyperactivation leads to pathological outcomes. In contrast, in peripheral nerve injury models, precisely timed c-Jun activation triggers regenerative gene programs that are critical for axonal regrowth. These opposing effects emphasize the need for spatiotemporal precision in therapeutically targeting this pathway. This review integrates findings from genetic, molecular, and pharmacological studies to clarify the dual contributions of c-Jun to neuroregenerative and neurodegenerative processes. Emerging therapeutic strategies, such as isoform-selective JNK inhibitors, hold promise for harnessing the potential of c-Jun. A deeper understanding of the role of c-Juns could significantly enhance the efficacy of pharmacological interventions to improve neurological outcomes in neurodegenerative diseases.

Keywords: c-Jun; Activator protein 1; Neuronal apoptosis; Neuroregeneration; Neurogenesis; Neurodegenerative diseases

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1. Introduction

Neurodegenerative disorders of the central nervous system (CNS), including Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and multiple sclerosis, result from chronic, progressive degeneration of neural tissue, leading to the loss of neurons or glial cells. Neural stem cells (NSCs) offer potential for treating neurodegenerative diseases, stroke, and spinal cord injuries due to their self-renewal and differentiation capabilities.¹⁻³ Despite promising research, practical challenges limit their clinical applications. In mammals, neurogenesis is primarily restricted to the subventricular zone (SVZ) of the dentate gyrus and the subgranular zone, with limited NSC differentiation into neurons.⁴ One promising approach to enhance CNS regeneration involves identifying compounds that promote NSC differentiation. Organic molecules, such as retinoic acid, and protein factors, such as nerve growth factor (NGF) and insulin-like growth factor, upregulate key transcription factors and signaling pathways to accelerate differentiation.^{5,6}

As a member of the activator protein 1 (AP-1) transcription factor family, c-Jun is a potent transcriptional activator.⁷ Its overexpression is frequently observed during development, in adults, and in injured nervous systems. During neuronal differentiation, as well as embryonic and postnatal neuronal survival, c-Jun gene and protein expression, along with its phosphorylation, are significantly upregulated.^{8,9} c-Jun plays a critical role in neuronal processes, including apoptosis, neurogenesis, and axonogenesis, which are pivotal in both neurodegeneration and neural regeneration.^{7,10}

The upregulation of c-Jun often coincides with the activation of related transcription factors, such as Jun-B, Jun-D, Fos family members (Fos, FosB, Fra-1, Fra-2), or activating transcription factor (ATF)-family proteins.¹¹ Notably, c-Fos expression markedly increases following trans-synaptic stimulation.⁷ Studies involving c-Jun deletion or dominant-negative constructs have indicated that c-Jun is the primary AP-1 transcription factor responding to neural injury.¹² Despite over two decades of research, c-Jun remains central to a complex molecular network governing neuronal functions, with some mechanisms still not fully understood. This article explores the role of c-Jun in neurogenesis, axonal development, and neurodegenerative processes, with a focus on its structural characteristics and regulatory mechanisms.

2. c-Jun as a member of the AP-1

The Jun protein was first identified in transformed cells containing the replication-deficient avian sarcoma virus 17 genome, which encodes a 65 kDa gag-Jun fusion protein,

v-Jun. Subsequently, its homolog, the proto-oncogene c-Jun, was identified in human and mouse tissues.¹³ c-Jun shares sequence similarity with v-Jun and the yeast transcriptional regulator general control non-derepressible 4 (GCN4). Initially, GCN4 and mammalian AP-1 were recognized as transcription factors that bind to a specific enhancer sequence with shared DNA-binding specificity. Using this DNA fragment in affinity chromatography, researchers co-purified c-Jun with c-Fos, identifying AP-1 as a c-Jun/c-Fos heterodimer.^{7,14} Jun proteins also form heterodimers with other transcription factors, including ATF-family proteins and other basic leucine zipper (bZIP)-containing transcription factors.^{15,16}

As a core component of the AP-1 complex, c-Jun is the most potent transcriptional activator,⁹ regulating various cellular processes, such as proliferation, apoptosis, survival, and tumorigenesis. Through interactions with diverse signaling pathways, c-Jun modulates gene expression patterns that determine cell fate, making it essential in both physiological and pathological conditions.

A regulatory feedback loop exists wherein AP-1 stimulates *Jun* promoter activity and gene expression, while elevated c-Jun levels further enhance AP-1 activity, reinforcing its own transcription.¹³ This autocrine feed-forward mechanism allows c-Jun to convert transient biochemical signals into sustained AP-1 activation, enabling long-term regulation of biological processes.⁷ Conversely, persistent c-Jun expression is critical for maintaining AP-1 activity. This interplay underscores the complexity of the c-Jun/AP-1 signaling network and c-Jun's pivotal role in mediating cellular responses to stimuli.

The activity of AP-1 is strongly upregulated by stimuli such as growth factors, cytokines, and extracellular stressors, enhancing c-Jun's DNA-binding capacity and transcriptional activity.⁷ This process is initiated by a signal transduction cascade that triggers rapid c-Jun phosphorylation by Jun N-terminal kinases (JNKs), occurring within minutes without requiring new protein synthesis.^{17,18} Phosphorylation at serine residues 63 and 73 and threonine residues 91 and 93 in c-Jun's transactivation domain enhances target gene transcription, including the *Jun* gene itself.¹⁹

Although phosphorylation initiates AP-1 activation, phosphorylated c-Jun is unstable and transient. Its instability limits its ability to sustain prolonged AP-1 activity. However, phosphorylation enhances c-Jun's promoter-binding affinity, influencing gene regulation. Stimulus-induced AP-1 activation increases *Jun* promoter activity, and the resulting rise in c-Jun expression further reinforces AP-1 function, establishing a self-sustaining regulatory loop.²⁰

3. c-Jun-related signaling pathway

Early research focused mainly on the structural and functional characterization of c-Jun, establishing it as a bZIP transcription factor.²¹ Subsequent studies showed that extracellular signals can trigger post-translational modifications of c-Jun, thereby regulating its transcriptional activity and downstream gene expression. More recent work has uncovered a complex, multi-layered regulatory network, in which c-Jun mediates signal integration, amplification, and crosstalk among pathways controlling tissue development and disease progression.¹⁹ One regulatory mechanism involves an autocrine amplification loop, in which stimulus-driven AP-1 activation induces *Jun* transcription, and the resulting increase in c-Jun further potentiates AP-1 activity.

In addition, studies in *Jun*-knockout mice have shown that c-Jun acts as a central integrator of multiple developmental signaling pathways, including mitogen-activated protein kinase (MAP3K)–JNK, epidermal growth factor receptor (EGFR)–extracellular signal-regulated kinase (ERK), and EGFR–Ras homolog family member A (RhoA)–Rho-associated protein kinase (ROCK), all of which are critical for proper neuron development.^{13,22} The MAP3K–JNK–c-Jun axis represents a primary pathway in which stress stimuli activate JNK through upstream mitogen-activated protein kinase (MKK)4/7, leading to c-Jun phosphorylation at Ser-63/73 and subsequent modulation of AP-1-dependent transcription.^{19,23} Activation of JNK through phosphorylation triggers the AP-1 transcription factor complex, which consists of Jun (*Jun/Jra*) and Fos (*Fos/Jay*) family members.^{7,12} In turn, AP-1 regulates the expression of numerous target genes, thereby modulating various biological processes.^{7,24–26}

Concurrently, the EGFR–ERK pathway mediates c-Jun phosphorylation through ERK1/2 activation. Studies have shown that ERK can modulate c-Jun through the p70 S6 kinase–glycogen synthase kinase 3 beta (GSK-3 β) pathway, facilitating the C-terminal dephosphorylation of c-Jun and thereby enhancing its DNA-binding activity.^{27,28} GSK-3 phosphorylates c-Jun at its C-terminus, maintaining it in a DNA-unbound state.^{29,30} The functional connection between ERK and c-Jun has also been demonstrated in fission yeast, where the mammalian homologs ERK and Jun coordinate cellular elongation immediately following cell division.²²

While RhoA–ROCK signaling regulates c-Jun expression via both JNK-dependent mechanisms and alternative effectors, including protein kinase N (PKN) and ERK6, c-Jun is required for RhoA-mediated cellular transformation. It is proposed that RhoA may coordinate the PKN–ERK6 pathway with cytoskeletal regulatory

signals to drive c-Jun transcription.³¹ In addition, inhibition of ROCK nearly abolished RhoA's ability to activate the *Jun* promoter and induce c-Jun expression. These findings support the existence of a distinct RhoA–ROCK–JNK signaling axis, wherein JNK phosphorylates and activates c-Jun and ATF2 bound to the AP-1 site of the *Jun* promoter, thereby enhancing transcription.³² These interconnected pathways collectively enable c-Jun to process diverse extracellular signals and translate them into specific transcriptional programs. Although c-Jun has been extensively studied for over 20 years, it remains a central element in a complex molecular network, with many of its functional roles yet to be fully understood (Figure 1).

4. c-Jun-related neuronal regulation

The transcription factor c-Jun is an early and consistent marker of neurons responding to nerve-fiber transection, associated with both degeneration and survival. *In vitro* studies have shown that c-Jun expression induces apoptosis in neonatal neurons; however, in the adult nervous system, it may promote neuroprotection and regeneration. The functional duality of c-Jun positions it as a pivotal regulator of neuronal death or survival not only in response to axonal lesions but also in neurodegenerative disorders.¹⁶

In mammals, the JNK signaling pathway is highly active in the CNS compared to other tissues. It is encoded by three genes: *Jnk1*, *Jnk2*, and *Jnk3*. While *Jnk1* and *Jnk2* are expressed ubiquitously, *Jnk3* is primarily expressed in the brain, testis, and smooth muscles. Proteins regulated by JNK-mediated phosphorylation are critical for understanding JNK's effects in neurons. JNK activities in cytoplasmic and nuclear compartments respond differently to stress, differentiation, maturation, and neurite outgrowth. For example, *JNK3*, the most prominent isoform in the CNS, is implicated in neural cell deterioration and synaptic dysfunction, making it one of the earliest factors linked to neurodegenerative and neurodevelopmental disorders.^{33–35} Thus, *JNK3* is a key mediator of neuronal death in neurodegenerative diseases and a promising therapeutic target for CNS-related conditions.

4.1. c-Jun and neuronal death

Neuronal cell death is characterized by activation of the JNK pathway and rapid upregulation of its downstream target, the AP-1 transcription factor c-Jun.^{16,36} While JNK signaling is essential for neuronal apoptosis, elevated JNK activity under normal physiological conditions suggests that it also plays roles in other neuronal metabolic processes.^{36,37} Pharmacological and genetic studies have indicated that JNK is critical for the death of cerebellar

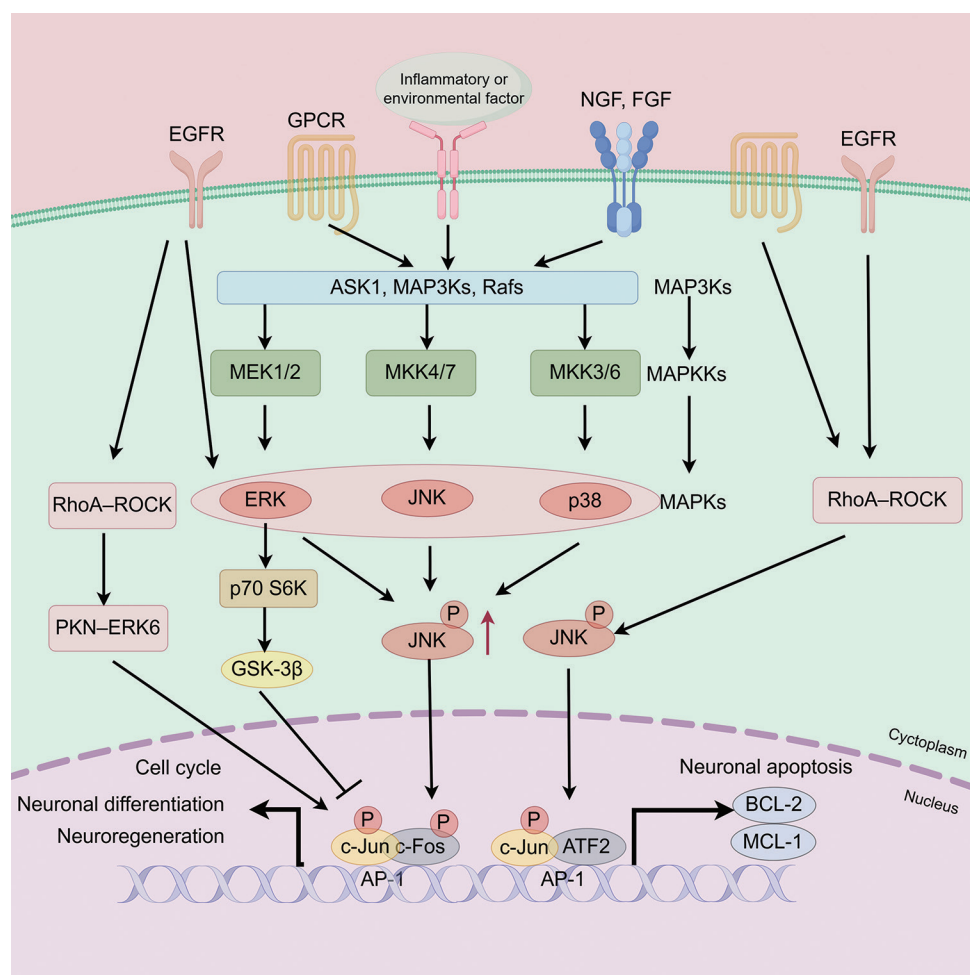


Figure 1. c-Jun serves as a central node that integrates key signaling pathways to regulate cell fate decisions. JNK regulates cell cycle progression, neuronal differentiation, neuroregeneration, and apoptosis via different signaling pathways. Together, JNK and ERK, along with p38, constitute three separate groups of MAPK that directly phosphorylate and activate c-Jun in response to inflammatory cytokines or environmental factors, through extracellular signaling mediated by the protein kinase cascade in the cytoplasm. In parallel, the EGFR-ERK pathway enhances c-Jun's DNA-binding ability by inhibiting GSK-3 β -mediated C-terminal phosphorylation. Furthermore, the RhoA-ROCK pathway regulates *Jun* transcription through both JNK-dependent and alternative mechanisms (e.g., PKN/ERK6). These interconnected networks allow c-Jun to translate diverse extracellular cues into specific transcriptional programs that govern development and cellular responses by regulating the cell cycle, neuronal differentiation, and neuronal apoptosis. Created with FigDraw.com. Shuo Zhang, 2025. Copyright Code: AIAOOB7ec0.

Abbreviations: AP-1: Activator protein 1; ASK1: Apoptosis signal-regulating kinase 1; ATF2: Activating transcription factor 2; BCL-2: B-cell lymphoma 2; EGFR: Epidermal growth factor receptor; ERK: Extracellular signal-regulated kinase; FGF: Fibroblast growth factor; GPCR: G protein-coupled receptor; GSK-3 β : Glycogen synthase kinase 3 beta; JNK: c-Jun N-terminal kinase; MAP3K: Mitogen-activated protein kinase; MAPKK: Mitogen-activated protein kinase; MCL-1: Myeloid cell leukemia 1; MEK1/2: Mitogen-activated protein kinase 1 and 2; MKK: Mitogen-activated protein kinase; NGF: Nerve growth factor; PKN: Protein kinase N; ROCK: Rho-associated protein kinase.

granule neurons, but AP-1 and c-Jun do not predominantly drive apoptosis. Instead, c-Jun phosphorylation is vital for JNK-mediated neurotoxicity. The stability of JNK pathway components tightly regulates the balance between apoptosis and differentiation in NSCs. For example, the absence of F-box and WD repeat domain-containing 7 (FBW7) increases the levels of phosphorylated c-Jun, triggering neuronal apoptosis.³⁸ Studies have demonstrated that microinjection of antibodies which neutralize c-Jun can delay the apoptosis of sympathetic neurons caused by NGF

deprivation.^{39,40} *In vitro* studies have confirmed the role of c-Jun in neuronal death, as its overexpression induces apoptosis, whereas the expression of a dominant-negative *Jun* or targeted deletion blocks death in sympathetic neuronal cultures.^{36,41-43} However, in non-neuronal systems, c-Jun expression can protect against cellular damage and prevent death.⁴⁴ Recent studies have confirmed c-Jun as a pro-apoptotic factor in sympathetic and cerebellar granule neurons, with phosphorylation promoting apoptosis, although not strictly required.^{16,45} Mutations at *Jun*'s

N-terminal phosphorylation sites significantly reduce neuronal apoptosis, likely by impairing activation of pro-apoptotic transcriptional targets, including c-Jun itself, which is autoregulated.³⁶

The role of c-Jun in neuronal apoptosis is well-documented across contexts. Dopamine-mediated JNK activation and c-Jun phosphorylation induce neuronal apoptosis.⁴⁶ Namgung and Xia⁴⁷ demonstrated that *JNK3* and p38 MAPK mediate arsenite-induced apoptosis in cortical neurons. Wong *et al.*⁴⁸ showed that both the JNK/c-Jun and p53 pathways drive cortical neuronal apoptosis induced by arsenite. B-cell lymphoma 2 (BCL-2) family members are critical for neuronal survival, with the pro-apoptotic protein BCL-2-associated X (BAX) being essential for cell death in sympathetic and cerebellar granule neurons.⁴⁹ BAX activity is regulated by BCL-2 homology 3-only proteins, such as BCL-2-interacting mediator of cell death (BIM) and death protein 5, which are upregulated during neuronal death.⁵⁰ Akhter *et al.*⁵¹ highlighted JNK/c-Jun-mediated regulation of pro-apoptotic proteins BIM and p53 upregulated modulator of apoptosis in amyloid-beta (A β)-treated neurons.

4.2. c-Jun and neurogenesis

Neurogenesis is a critical process in CNS development. In the embryonic brain, *Jun* messenger RNA (mRNA) is highly expressed in the periventricular germinal layer, the precursor to the adult SVZ, which houses neural precursor cells (NPCs). Nearly all proliferating embryonic NPCs express c-Jun, but only about half of adult NPCs are c-Jun immunopositive.⁵² c-Jun is rarely detected in post-mitotic migrating neurons in the embryonic brain. In contrast, most c-Jun-positive cells in the adult brain are tangentially migrating neurons destined for the olfactory bulb. Persistent epilepsy increases transient NPC proliferation without significantly altering c-Jun expression, suggesting that c-Jun plays a critical role in embryonic NPC proliferation but distinct functions in adult neurogenesis.^{52,53}

Neural precursor cells in the germinal layer proliferate during gestation, with young neurons migrating radially or tangentially to their destinations.⁵⁴ c-Jun is detectable in proliferating cells of the SVZ and the telencephalic ventricular zone, as confirmed by immunohistochemistry and *in situ* hybridization.^{55,56} These findings suggest that c-Jun regulates the cell cycle of proliferating NSCs in the embryonic brain. Postnatally, c-Jun expression persists in the germinal layer surrounding the lateral ventricles.⁵² However, its expression pattern in the adult brain differs, indicating distinct roles in embryonic versus adult neurogenesis.

In the adult SVZ–rostral migratory stream–olfactory bulb system, c-Jun may facilitate NPC migration. Adult

SVZ NSCs exhibit regional specificity and diverse differentiation fates.⁵⁷ c-Jun may have unique roles in small NPC subpopulations, although the lack of specific markers complicates analysis. Notably, nearly half of the newly generated cells undergo apoptosis.^{58,59} Given the role of c-Jun in JNK-mediated apoptosis and the presence of phosphorylated JNK in the SVZ, c-Jun may contribute to eliminating newly generated cells in the SVZ and rostral migratory stream. However, the low number of terminal deoxynucleotidyl transferase dUTP nick-end labeling-positive apoptotic cells compared to c-Jun+ cells suggests limited c-Jun-induced cell death.⁵⁸ Thus, c-Jun potentially plays distinct roles in embryonic and adult NPCs, with a critical function in embryonic NPC proliferation.⁶⁰

In the adult hippocampal dentate gyrus, neurogenesis enables the continuous generation of neurons. JNK activity regulates cell proliferation and differentiation, with *JNK1* and *JNK3* controlling glial fibrillary acidic protein (GFAP)-positive/sex-determining region Y-box 2-positive early progenitor cells, but not GFAP-positive/Nestin-positive cells. In addition, *JNK1* deficiency increases the number of immature neurons (e.g., doublecortin-positive and polysialylated neural cell adhesion molecule-positive neurons) compared to wild-type.⁶⁰

4.3. c-Jun and neuronal differentiation

NSCs can self-renew and differentiate into oligodendrocytes, astrocytes, and neurons, making them promising candidates for treating CNS injuries.^{61–63} Neuronal differentiation is a critical step in neuronal regeneration and replacement.^{64–66} However, NSCs produce few neurons under normal conditions, necessitating strategies to enhance differentiation.

The JNK proteins, upstream of c-Jun, regulate cell survival, apoptosis, and differentiation.⁶⁷ Accumulating evidence highlights JNK's role in embryogenesis, neuronal synapse formation, growth, and differentiation.^{68–71} Comparative gene expression analyses between undifferentiated human embryonic stem cells (ESCs) and their differentiated counterparts reveal the downregulation of JNK pathway genes (e.g., *Map4k1*, *Map3k7*, and *Jun*) during differentiation, suggesting that JNK activation maintains the undifferentiated state.⁷² Clustered regularly interspaced short palindromic repeats/CRISPR-associated proteins (CRISPR/Cas) screens identified *Jnk–Jun* family genes as inhibitors of endoderm differentiation.⁷³

Fibroblast growth factor promotes ESC differentiation into primitive neuroepithelial cells through JNK and ERK pathways, with *JNK1* and ERK2 playing significant roles.⁷⁴ Studies on *Jnk1*^{−/−} ESC lines confirmed *JNK1*'s critical role, as these cells failed to undergo neuronal

differentiation.⁷⁵ Differentiation-inducing factors, such as retinoic acid, NGFs, and cytokines (e.g., interferon- γ and interleukin [IL]-1 β), activate the JNK pathway. Specifically, retinoic acid enhances JNK signaling by stimulating transcription factors (e.g., signal transducer and activator of transcription 1 and 2 [STAT1/2], cyclic adenosine monophosphate response element-binding protein [CREB], and ATF2), thereby promoting neuronal development.^{66,76} IL-1 β supports NPC differentiation via the Wnt/JNK pathway.⁷⁷ In PC12 cells, NGF activates JNK signaling through neurotrophic receptor tyrosine kinase 1, upregulating differentiation-related genes in collaboration with small GTPases (G α , Ras, and cell division control protein 42 homolog) and actin-binding proteins.⁷⁸ Introducing JNK3-p54 into PC12 cells has been shown to enhance c-Jun phosphorylation, resulting in increased neurite length and number following NGF stimulation.⁷⁹

The role of c-Jun in cellular responses is complex, influenced by its expression levels, dimerization partners, and interactions with transcription factors, co-activators, and co-repressors. FBW7, a component of the S-phase kinase-associated protein 1–cullin1–F-box protein E3 ubiquitin ligase complex, regulates c-Jun and Notch stability via ubiquitination and proteasomal degradation.^{80,81} The absence of FBW7 increases phosphorylated c-Jun levels, inducing neuronal apoptosis. In addition, AP-1 also induces Notch expression, and balanced levels of phosphorylated c-Jun and Notch are critical for neuronal differentiation. FBW7 thus plays a vital role in regulating neuronal differentiation by counteracting Notch and JNK/c-Jun signaling.^{38,80} These interactions finely tune the balance between apoptosis, survival, and differentiation^{13,41,45} (Figure 2).

4.4. c-Jun in neuronal survival and axon regeneration

The c-Jun protein contributes to neuroprotection and regeneration, with some axotomized neurons surviving despite high c-Jun levels. CNS axons have limited regenerative capacity, hindering functional recovery post-injury due to the inability to reactivate regeneration-associated transcriptional programs.^{82,83} Transcription factors, such as c-Jun, are promising candidates for promoting regeneration by regulating multiple regeneration-associated genes.^{84,85} Inducing the expression of transcription factors can enable regeneration in injured CNS neurons.⁸⁶

Emerging evidence underscores the role of c-Jun in axon regeneration. In peripheral nerve injury models, transient c-Jun activation upregulates growth-associated protein 43 (GAP-43) and integrin expression, promoting

axonal sprouting. A JNK3-specific inhibitor has been demonstrated to preserve this regenerative function while preventing excessive c-Jun activity, offering a balanced therapeutic approach.⁸⁷ Besides, c-Jun/ATF3 heterodimerization enhances neurite outgrowth in dorsal root ganglion (DRG) neurons by activating GAP-43 transcription. In spinal cord injury models, c-Jun/ATF3 overexpression improves functional recovery, suggesting the potential for CNS regeneration.⁸⁸ These findings highlight c-Jun's context-dependent regenerative capacity, which requires precise modulation to prevent degenerative outcomes.

Peripheral axon regeneration involves the rapid, sustained upregulation of transcription factors, such as c-Jun. Axotomized peripheral neurons co-express c-Jun and GAP-43 during regeneration, with enhanced c-Jun expression in fetal tissue grafted into adult striatum persisting up to six months. In contrast, c-Jun remains uninduced in the CNS when axotomy fails to trigger neuronal regeneration.¹⁶ Raivich *et al.*¹² provided genetic evidence that c-Jun is essential for efficient axon regeneration *in vivo* using a nervous system-specific mutant. While *Jun* deletion significantly impairs axon regeneration, its impact on developmental axon growth is minimal, indicating distinct genetic programs for adult regeneration versus embryonic growth.⁸⁹ Neurotrophic factors, critical for embryonic axon growth, are unlikely to drive c-Jun-mediated transcription during development; however, c-Jun activation post-NGF withdrawal triggers apoptosis.³⁹

Axon regeneration is vital for functional recovery post-spinal cord injury. Within the AP-1 complex, c-Jun drives the transcriptional response in DRG neurons to peripheral axon injury, facilitating regeneration.⁹⁰ Danzi *et al.*⁸⁸ hypothesized that distinct Jun dimers favor specific motifs. Still, they found that post-injury binding sites often feature cyclic adenosine monophosphate response element or lack Jun-related motifs, suggesting chromatin accessibility or overall Jun activity outweighs motif affinity.⁸⁸ ATF3/c-Jun dimerization enhances axon growth in cortical and hippocampal neurons, with synergistic effects in peripheral neurons.

In hippocampal and DRG neurons, the signaling environment enables overexpressed monomers to form active dimers, promoting neurite outgrowth, which is absent in cortical neurons.⁸⁸ Comparative analyses identified STAT3 as a key regulator of axon growth in DRG neurons.^{91–93} Lerch *et al.*¹⁰ showed that c-Jun paired with STAT6 boosts neurite length in cortical neurons. In cortical section cultures, c-Jun alone or with STAT6 promotes growth. GAP-43 and integrins, which are potential c-Jun

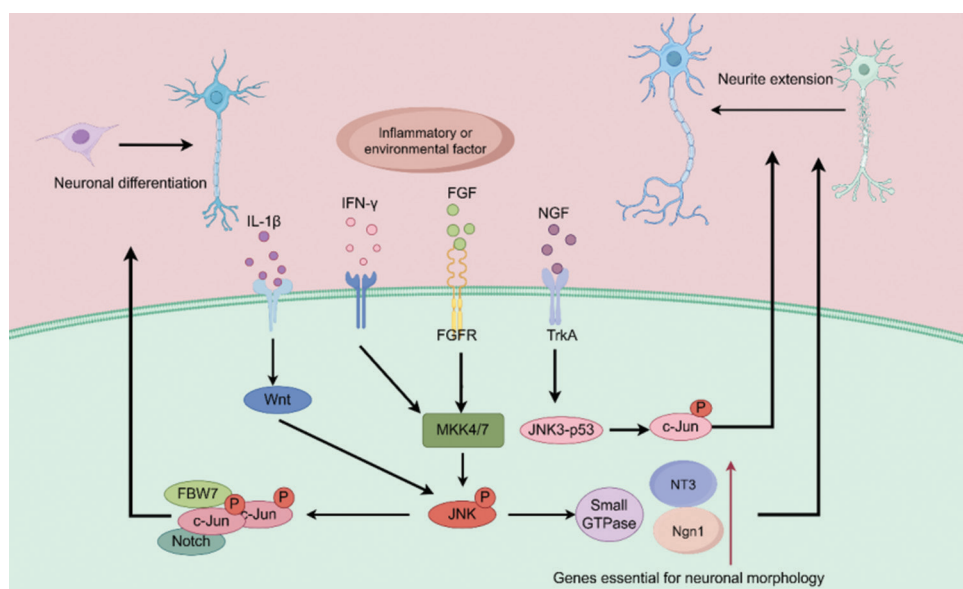


Figure 2. The role of the JNK signaling pathway in neuronal differentiation and neurite extension. Multiple developmental signals, including FGF, IFN- γ , and NGF, converge to activate the MKK4/7–JNK/c-Jun pathway, which is essential for driving neuronal differentiation from progenitor cells and neurite extension. On the one hand, activated JNK can stimulate the high expression of neurotrophic factors, such as NT3 and Ngn1, to promote neurite outgrowth. JNK3–p53 enhances c-Jun phosphorylation, increasing neurite length. Meanwhile, JNK activation induces the expression of Notch. FBW7 maintains a balance between phosphorylated c-Jun and Notch, which are critical for neuronal differentiation. Created with FigDraw.com. Shuo Zhang, 2025. Copyright Code: UUTUI624a3.

Abbreviations: FBW7: F-box and WD repeat domain-containing 7; FGF: Fibroblast growth factor; FGFR: Fibroblast growth factor receptor; IFN- γ : Interferon-gamma; JNK: c-Jun N-terminal kinase; IL-1 β : Interleukin 1-beta; MKK4/7: Mitogen-activated protein kinase 4 and 7; NGF: Nerve growth factor; Ngn1: Neurogenin 1; NT3: Neurotrophin-3; TrkA: Tropomyosin receptor kinase A.

transcriptional targets, play a critical role in regeneration. GAP-43 overexpression promotes axon growth, while $\alpha 7$ integrin mutation blocks peripheral nerve regeneration *in vivo*.^{94–96} Furthermore, c-Jun enhances axon growth in CNS neurons by increasing *GAP43* or integrin $\alpha 7$ mRNA expression.¹⁰

Regenerative axon growth relies on activating growth programs through gene transcription and local signaling cascades. Nuclear translocation of c-Jun and subsequent gene transcription depend on JNK activity.¹⁶ *JNK1* also phosphorylates axon cytoskeleton proteins (e.g., microtubule-associated proteins [MAP]-1B and MAP2), enhancing microtubule binding and regulating local microtubule assembly.⁹⁷ Inhibiting JNK-induced doublecortin phosphorylation disrupts axon growth, indicating JNKs synchronize c-Jun-mediated gene expression with local regeneration.⁹⁸

5. c-Jun and neurodegenerative diseases

5.1. c-Jun in AD

AD, the leading neurodegenerative disorder, is characterized by progressive memory loss, cognitive impairment, and neuronal damage, with a prevalence estimated at 40.19% in older populations.^{99–101} While symptoms can be

mitigated, there is currently no cure for this condition. AD pathology involves the formation of neurofibrillary tangles (NFTs) and the deposition of A β peptide in cortical and hippocampal neurons.^{100–102} Hypotheses explaining AD etiology include the amyloid hypothesis, tauopathy, cholinergic dysfunction, mitochondrial impairment, and neuroinflammation, with the amyloid hypothesis being the most prominent.¹⁰³ Amyloid precursor protein (APP), a transmembrane protein in neurons, is cleaved by secretases to produce A β .^{104,105} Meanwhile, intracellular NFTs, formed by hyperphosphorylated tau protein, disrupt microtubule stability, impairing axonal transport.¹⁰⁶

The JNK signaling pathway drives neuronal injury, synaptic loss, and memory impairment in AD. Early JNK activation in excitatory postsynaptic dendritic spines promotes synaptic loss. In AD models, *JNK* knockdown reduces synaptic loss, A β deposition, tau phosphorylation, neuronal apoptosis, and neuroinflammation.^{35,107,108} JNK regulates APP processing and metabolism, amplifying A β production. Moreover, *JNK3*, a CNS-enriched isoform, phosphorylates APP at Thr668, thereby enhancing its internalization and β -secretase (beta-site APP cleaving enzyme 1 [BACE1])-mediated cleavage, which produces neurotoxic A β 42, a key component of senile plaques.^{109–112} Chronic hypoxia upregulates hypoxia-

inducible factor 1- α via the JNK pathway, increasing BACE1 expression and exacerbating A β production.¹¹³ A β reciprocally activates JNK through AMP-activated protein kinase/mammalian target of rapamycin (mTOR) inhibition and endoplasmic reticulum stress, forming a positive feedback loop that perpetuates neuronal damage.¹⁰⁹

Altering the JNK pathway also disrupts cellular survival mechanisms. Elevated A β impairs mTOR signaling, thereby hindering lysosomal function and autophagic clearance, both of which further promote A β accumulation.^{114,115} Oxidative stress and NFT-induced microtubule changes activate the intrinsic apoptotic pathway, which is regulated by the BCL-2 family, comprising pro-apoptotic proteins (e.g., BAX, BCL-2 homologous antagonist/killer, BCL-2-associated death promoter, and BCL-2 homology 3 interacting-domain death agonist) and anti-apoptotic proteins (e.g., BCL-2, BCL-XL, and myeloid cell leukemia 1 [MCL-1]).^{116,117} JNK phosphorylates BCL-2 and MCL-1, inhibiting their anti-apoptotic activity, and downregulates BCL-w, triggering mitochondrial release of second mitochondria-derived activator of caspases, which activates caspase-9 and drives A β -induced apoptosis.^{118,119} JNK thus serves as a convergence point for autophagy failure and apoptosis, highlighting its dual role in AD neurodegeneration.¹¹⁰

The JNK pathway also promotes tau hyperphosphorylation, contributing to NFT formation.^{120,121} JNK inhibition prevents tau phosphorylation in rat cortical neurons and transgenic AD mice (TgCRND8).¹²⁰ JNK isoforms differentially phosphorylate tau: *Jnk2* targets S422 (an early AD biomarker), *JNK1* phosphorylates S199/T212, and *JNK3* drives hyperphosphorylation at S202/S422, accelerating NFT maturation.¹²² Phosphorylated tau dissociates from microtubules, impairing axonal transport and autophagosome-lysosome fusion, promoting toxic protein aggregation. Furthermore, JNK induces insulin resistance by serine phosphorylating insulin receptor substrate 1, activates GSK-3 β , and exacerbates amyloid and NFT pathology.¹²³ Systemic insulin resistance, driven by *JNK1/JNK3*-mediated pancreatic β -cell dysfunction, synergizes with A β pathology.¹²⁴ JNK stabilizes phosphorylated c-Jun, facilitating its incorporation into NFTs and perpetuating AD progression. These mechanisms position *JNK3* as a critical node linking tauopathy, A β pathology, and insulin resistance, offering a multifaceted therapeutic target.^{33,109,124}

Neuroinflammation, a key AD driver, involves microglia-mediated innate immune responses.¹²⁵⁻¹²⁷ Microglia clear A β through toll-like receptors (TLR; e.g., TLR2 and TLR4), but their activation also releases

proinflammatory mediators (e.g., IL-1 β , IL-6, tumor necrosis factor- α [TNF- α], prostaglandin E2, nitric oxide [NO], brain-derived neurotrophic factor [BDNF]),¹²⁸ stimulating JNK and AP-1 to upregulate genes such as Cyclooxygenase 2, NO synthase 2 (NOS2), and C-C motif ligand 2 (CCL2).¹²⁹ Moreover, microglia also exacerbate pathology through IL-1 production and p38-MAPK activation, driving synaptic and cytoskeletal damage.^{129,130} Recent studies have highlighted the role of c-Jun in various neurodegenerative diseases. In AD, c-Jun drives the mobilization of transposable elements via the cyclic GMP-AMP synthase-stimulator of interferon genes (STING) pathway, triggering neuroinflammation and neuronal death; its inhibition reduces these effects.¹³¹ In ALS, *JNK3*-mediated c-Jun phosphorylation upregulates pro-apoptotic genes (*BIM* and *BAX*) in *SOD1* mutant mice, accelerating motor neuron degeneration, with *JNK3* or *Jun* knockdown extending survival.¹³² In multiple sclerosis, microglial c-Jun promotes the expression of CCL2 and NOS2, thereby exacerbating inflammatory demyelination in experimental autoimmune encephalomyelitis models, while c-Jun inhibition ameliorates disease severity.¹³³

The JNK inhibitor SP600125 reduces neuronal death in AD models but lacks isoform specificity and binds to unrelated kinases.^{87,134} *JNK3*'s role in A β 42 generation and autophagic/apoptotic cascades makes *JNK3*-selective inhibitors promising for disrupting AD pathology.^{24,53} Other JNK inhibitors have also shown *in vitro* promise but require further investigation for specificity and toxicity^{110,134} (Figure 3).

5.2. c-Jun in HD

HD, a lethal neurodegenerative disorder, involves striatum- and cortical-projection neuron degeneration, causing motor, cognitive, and behavioral decline.¹³⁵ Typically, onset occurs between ages 35 and 45, with progressive brain atrophy leading to death, as treatments cannot halt progression.^{136,137} HD is caused by an expanded polyglutamine (polyQ) repeat in the Huntington protein (HTT), triggering protein aggregation and neuronal death.¹³⁶

In HD models, polyQ-HTT activates the JNK pathway, increasing *JNK3* activity, which in turn phosphorylates motor protein-1, thereby disrupting axonal transport and microtubule stability.^{138,139} In a rat HD model, a kinase inhibitor has been demonstrated to suppress JNK activity, reduce brain damage, and provide neuroprotection.¹⁴⁰ These findings position JNK as a key therapeutic target, although further studies are needed to elucidate its role in HD progression.

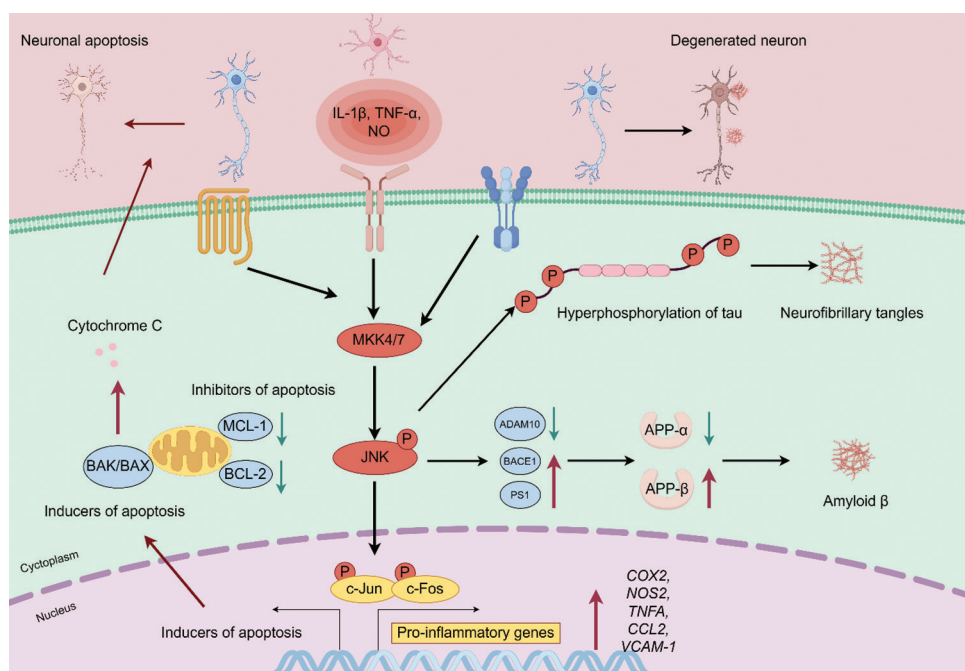


Figure 3. The multifaceted role of the JNK pathway in AD. When stimulated by external factors, microglia produce inflammatory mediators, such as IL-1 β , IL-6, TNF- α , and NO, thereby activating the JNK pathway. The JNK pathway is involved in the pathophysiological process of AD through its pro-inflammatory effects, which are mediated by AP-1 and result in the high expression of pro-inflammatory genes, such as COX2, NOS2, TNFA, CCL2, and VCAM1. On the other hand, JNK phosphorylation promotes the downregulation of anti-apoptotic proteins, such as BCL2 and MCL-1, which in turn leads to neuronal apoptosis. In addition, JNK also plays a direct role in the formation of neurofibrillary tangles through tau phosphorylation, helping to regulate the formation of paired helical filaments and the proteolytic cleavage process. The JNK signaling pathway also facilitates β -secretase (BACE1)-mediated cleavage of APP, resulting in the generation of neurotoxic A β 42, a significant component of senile plaques and amyloid- β formation. Created with FigDraw.com. Shuo Zhang, 2025, Copyright Code: YOYII2fdd9.

Abbreviations: AD: Alzheimer's disease; ADAM10: A disintegrin and metalloproteinase domain-containing protein 10; APP: Amyloid precursor protein; BACE1: Beta-site APP cleaving enzyme 1; BAK: BCL-2 homologous antagonist/killer; BAX: BCL-2-associated X; BCL-2: B-cell lymphoma 2; IL: Interleukin; JNK: c-Jun N-terminal kinase; MCL-1: Myeloid cell leukemia 1; MKK: Mitogen-activated protein kinase; NO: Nitric oxide; PS1: Presenilin 1; TNF- α : Tumor necrosis factor- α .

5.3. c-Jun in PD

PD is one of the most prevalent neurological conditions among neurodegenerative disorders. The number and health burden of PD increase rapidly in China. It is estimated that China will account for nearly half of the population with PD worldwide by 2030.¹⁴¹ The primary pathological feature of PD is the extensive loss of dopaminergic neurons in the substantia nigra, resulting in a marked reduction in striatal dopamine, which contributes to disease progression.¹⁴² While the origins of its pathogenesis remain elusive, epidemiological research has identified specific environmental risk factors associated with an increased risk of developing PD.

The JNK signaling contributes to neuronal death in PD, and its inhibition shows therapeutic potential. JNK-mediated phosphorylation of AP-1, particularly c-Jun, increases transcriptional activity in response to cytokines, environmental stress, and growth factors.¹⁴³ The phosphorylation of c-Jun is linked to apoptosis

in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated mice.^{20,144,145} In cultured PC12 cells and sympathetic neurons, antisense inactivation of superoxide dismutase elevates oxidative stress and JNK activity.¹⁴⁶ MKK4 activation occurs in neurons exposed to MPTP and manganese, linking oxidative JNK activation to neurotoxin-induced dopaminergic neuron death.^{20,145,146} Meanwhile, JNK3 activation occurs in substantia nigra dopaminergic neurons following neurotoxin exposure in PD models.¹⁴⁷ JNK increases the BAX/BCL-2 ratio, disrupting BCL-2's protective role and triggering apoptosis and autophagy.¹⁴⁸ It has been shown that blocking JNK protects against PD-induced neurodegeneration.^{143,149} In addition, dopamine D1 receptor activation promotes JNK phosphorylation in striatal projection neurons, thereby mediating dopamine transmission during depletion and offering a potential avenue for PD treatment.¹⁵⁰

The role of the JNK pathway in stress-related processes in PD makes it a promising therapeutic target for the disease. Further exploration of its molecular mechanisms

will enhance the understanding of PD and identify targets for JNK inhibitors.

6. Future prospects

The c-Jun protein does not act alone; instead, it functions within a broader transcriptional network that includes STAT3, CREB, and ATF3—factors that cooperate or compete with c-Jun to fine-tune neuronal responses. STAT3 co-activation enhances regenerative programs, while CREB primarily supports survival and synaptic plasticity. In addition, ATF3, a canonical injury factor, frequently dimerizes with c-Jun to reinforce pro-regenerative transcriptional outputs. Disentangling how these factors shape c-Jun's transcriptional specificity remains critical for defining therapeutic windows that promote regeneration without triggering apoptosis.

A significant challenge lies in the tissue-specific and isoform-dependent actions of c-Jun. Chronic c-Jun activation exacerbates A β -driven synaptic loss in hippocampal neurons, whereas in olfactory ensheathing cells, it promotes the release of neurotrophic factors and remyelination.¹⁵¹ Such divergent effects potentially reflect context-specific interactions with binding partners, such as ATF2 and JunD, as well as modulation by post-translational modifications, including SUMOylation and ubiquitination. Future studies leveraging single-cell omics, spatial transcriptomics, and CRISPR-Cas9 perturbation screens will be essential for mapping c-Jun interactomes across neuronal subtypes and identifying the molecular switches that bias c-Jun toward neuroprotective or regenerative states.^{152,153}

Despite promising preclinical results, the clinical translation of JNK/c-Jun inhibitors remains limited. Most candidates, including SP600125, AS601245, and D-JNKI1, exhibit inadequate isoform specificity, poor blood–brain barrier penetration, and systemic toxicity arising from off-target kinase inhibition and interference with physiological JNK functions in metabolism and immunity.^{87,109,134} These shortcomings highlight the need for next-generation compounds with *JNK3* selectivity, optimized pharmacokinetics, and CNS-targeted delivery. Although exosomes and nanoparticle-based delivery systems have been proposed to enhance brain targeting, rigorous evaluation of their long-term biodistribution, immunogenicity, and drug-loading stability is still lacking. Dual-targeted strategies—such as pairing *JNK3* inhibitors with BDNF-mimetic peptides—may further enhance therapeutic specificity by simultaneously suppressing apoptosis and supporting synaptic resilience.⁸⁰

It is important to acknowledge the limitations of current experimental models in elucidating the c-Jun/JNK

signaling mechanisms that underlie neurodegeneration. Most mechanistic data are derived from acute injury paradigms and rodent or *in vitro* models, which only partially recapitulate the chronic, heterogeneous pathology of human neurodegenerative diseases. Interspecies differences (e.g., in proteotoxic stress accumulation and neuroinflammatory dynamics), simplified cellular environments that overlook critical intercellular crosstalk (such as microglia–astrocyte–neuron interactions), and supraphysiological perturbations constrain the direct translation of these findings to human CNS circuits and patients. In our opinion, these gaps contribute to longstanding challenges in translational research. Advancing human-induced pluripotent stem cell-derived models integrated with multi-omics profiling could help bridge the gaps by better emulating patient-specific contexts, ultimately guiding more precise therapeutic strategies.

7. Conclusion

Neurodegenerative disorders arise from progressive neuronal loss or myelin sheath deterioration, leading to neuron dysfunction. C-Jun, a core AP-1 transcription factor, integrates signals from stress-activated MAP3K–JNK, growth factor-driven EGFR–ERK, and cytoskeleton-modulating RhoA–ROCK pathways, orchestrating responses such as apoptosis and axon regeneration.^{7,13,53} In neurodegenerative diseases such as AD, PD, and HD, sustained JNK-mediated c-Jun phosphorylation drives neuronal death by upregulating pro-apoptotic genes (e.g., *BIM* and *FASL*) and disrupting mitochondrial integrity.¹¹⁰ Specifically, in AD, c-Jun exacerbates A β -induced synaptic loss and tau hyperphosphorylation, whereas in PD and HD, it promotes apoptosis and axonal transport deficits.^{33,109} Conversely, transient or injury-induced c-Jun activation supports axon regeneration in peripheral neurons and facilitates NSC differentiation by inducing growth-associated genes, such as *GAP43* and *STAT3*. These dualistic roles underscore the need for interventions that can selectively modulate the context-dependent functions of c-Jun.^{16,92}

Looking forward, several unresolved questions require attention. First, how can c-Jun be modulated in a cell-type- or region-specific manner to avoid compromising physiological functions? Second, can auxiliary factors such as JunD, ATF2, and epigenetic regulators be leveraged to decouple c-Jun's degenerative and regenerative mechanisms? Third, to what extent can combinatorial approaches—including gene editing, neurotrophic support, and artificial intelligence-guided target prediction—advance precision interventions? Finally, can biomarkers such as phosphorylated c-Jun in cerebrospinal

fluid aid in patient stratification for early-stage therapeutic intervention? Collectively, addressing these open questions will be essential for safely harnessing c-Jun's regenerative potential while mitigating its contribution to neurodegeneration.

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Conflict of interest

The authors declare that they have no competing interests.

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