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JNK pathway in CNS pathologies

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Abstract

The c-Jun N-terminal Kinase (JNK) signalling pathway is a conserved response to a wide range of internal and external cellular stress signals. Besides the stress response, the JNK pathway is involved in a series of vital regulatory mechanisms during development and adulthood that are critical to maintain tissue homeostasis. These mechanisms include the regulation of apoptosis, growth, proliferation, differentiation, migration and invasion. The JNK pathway has such a diverse functionality and cell-tissue specificity, that it has emerged as a key player in regeneration, tumorigenesis and other pathologies such as neurodegenerative diseases.

The JNK pathway is highly active in the central nervous system (CNS), and plays a central role for the cells to cope with pathophysiological insults during both development and adulthood. Among the many mechanisms described in the literature, in this review we focus on the JNK pathway functions in pathologies of the CNS. More specifically, we discuss some newly identified examples and mechanisms of JNK-driven tumor progression in glioblastoma, regeneration/repair after an injury in the CNS, neurodegeneration, and neuronal cell death. Recent studies have shown that the JNK pathway regulates matrix metalloproteinases (MMPs) production in response to cytoneme/tumor microtubes formation and Wingless (Wg)/WNT pathway activation in glioblastoma cells. Thus, JNK pathway is essential for glioblastoma progression, infiltration and non-autonomous induction of neurodegeneration. In regeneration, the JNK pathway controls *Draper* (*Drpr*) expression in glial cells that mediate engulfment and regeneration of the CNS upon injury.

Introduction

The Central Nervous System (CNS) is continuously exposed to stress stimuli during development, adulthood and under pathological aggressions. These events trigger mechanisms to integrate a cellular response and maintain homeostasis. Among these mechanisms, the Jun N-terminal kinase stress response signalling pathway (JNK), is a conserved Mitogen-Activated

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Protein Kinase (MAPK), that belongs to the stress-activated protein kinase (SAPK) group (J. M. Kyriakis & Avruch, 1990). It was defined as a group of kinases activated by internal or external stimuli that cause cell stress. Besides these stimuli, JNK pathway is activated after UV irradiation, glucose deprivation**,** DNA damage, heat stress, bacterial and viral infection, oxidative stress**,** inflammatory cytokines and growth factors (Finkel & Holbrook, 2000; Hamdi et al., 2005; Kamata et al., 2005; John M. Kyriakis & Avruch, 2001; Rosette & Karin, 1996; Song & Lee, 2007; Zanke et al., 1996).

The JNK pathway is activated by the ligand protein Eiger (Egr), the unique TNF superfamily member of ligands in *Drosophila* (Tatsushi Igaki et al., 2002; Moreno et al., 2002). Egr binds to the TNF Receptors TNFR) Grindewal (Grnd) (Sanchez et al., 2019), or Wengen (Wng) (T Igaki et al., 2009) that mediate the cascade of phosphorilations in JNK signalling pathway (La Marca & Richardson, 2020). Whereas there are differences between signalling pathway in mammals and flies, the molecular MAPK cascade presents high homology (Figure 1) (La Marca & Richardson, 2020). As a conserved signalling mechanism, *Drosophila* JNK cascade involves four kinases-step as well as human orthologues but with less diversity. A ligand binds to the receptor, in the case of *Drosophila* Egr ligand binds to Grnd or Wng receptors, that activates JNKKKs, while in mammals mitogens or cytokines induces MAP3K family activation (La Marca & Richardson, 2020). MAPK cascade triggers cytosolic JNK dual phosphorylation and initiates a pathway of cytosolic and nuclear substrates phosphorylation (Chang & Karin, 2001). Among targeted genes, cytoskeletal and mitochondrial proteins, nuclear transcriptions factors, membrane proteins, MAPs proteins, nuclear hormone receptors and even tau and the amyloid precursor protein have been described (Bogoyevitch & Kobe, 2006). Thus, gene expression derived from JNK activation leads in a control of cell survival or cell death depending on the cell type and the scenario (La Marca & Richardson, 2020). In mammals, the JNK pathway is encoded by *jnk1*, *jnk2* and *jnk3* (Bogoyevitch, 2006). JNK1 and JNK2 are ubiquitously expressed whereas JNK3 is restricted to the brain, cardiac smooth muscle and testis (Bogoyevitch, 2006; Coffey, 2014). In particular, JNK pathway is highly active in the CNS as compared with other tissues. Therefore, this signalling pathway emerges as a critical regulator of CNS cells under physiological and pathological conditions (Antoniou & Borsello, 2012; Yamasaki et al., 2012).

During early brain development, knockout experiments suggest a compensatory mechanism of the different JNK isoforms (reviewed in Yamasaki et al., 2012). However, they showed different temporal and regional pattern of expression (reviewed in (Coffey, 2014). Furthermore, a single deficiency for each isoform is viable with different phenotypes, highlighting the importance of each individual enzyme (reviewed in Yamasaki et al., 2012). Moreover, JNK regulates neurulation, neuronal cell proliferation, cell death, migration and axon-dendritic

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architecture through different species (Antoniou & Borsello, 2012; Coffey, 2014; Schellino et al., 2019; Sun et al., 2007; Yamasaki et al., 2012). Thus, perturbations in this signalling pathway cause developmental defects (Coffey, 2014; Schellino et al., 2019; Wang et al., 2007). Indeed, JNK controls brain programmed cell death in the adulthood in response to stress stimuli, regeneration, axonal transport, animal metabolism and behaviour (Coffey, 2014; B. P. Curran et al., 2003; Schellino et al., 2019; Yamasaki et al., 2012).

JNK pathway is conserved between mammals and insects (La Marca & Richardson, 2020). In *Drosophila*, JNK is encoded by a single gene: *basket* (*Bsk*), this simplifies the genetic studies that contributed to decipher the role of JNK under physiological and pathological stressful scenarios (Stronach & Perrimon, 1999; Yang et al., 2018). In *Drosophila* as in mammals, genetic expression after JNK signalling pathway mediates embryonic development, metabolism and growth, lifespan, programmed cell death, cell migration, repair and proliferation, immunity and axonal transport (Agnès et al., 1999; Horiuchi et al., 2007; Tatsushi Igaki, 2009; Nikoloudaki et al., 2020; Tafesh-Edwards & Eleftherianos, 2020). In addition, the literature reveals a dual role of JNK pathway in cell death and cell survival depending on the cell type and the context (La Marca & Richardson, 2020). This two-faded role is particularly important in CNS pathologies as neurodegeneration and tumorigenesis, that increase cellular stress-associated signals ((Musi et al., 2020; Portela et al., 2019). Here we review the role of JNK pathway in CNS pathologies and the contribution of both neurons and glial cells to glioblastoma tumor progression, regeneration/repair after an injury in the CNS, neurodegeneration, and neuronal cell death.

JNK in glioblastoma tumor progression

Glioblastoma multiforme (GB) is the most frequent and aggressive malignant primary brain tumor of the CNS in humans, with a frequency of 3 per 100,000/year (Gallego, 2015; Ostrom et al., 2015). Given the aggressiveness of the tumor and the resistance to current treatments, patients have a poor-prognosis and the median survival is limited to 12-15 months after the diagnosis (Furnari et al., 2007; Gallego, 2015; Ostrom et al., 2015). Although GB shows a high genetic heterogeneity, the molecular mechanisms that drive tumoral progression include common and conserved cellular and molecular features (Louis et al., 2016; Portela et al., 2019; Portela, Mitchell, & Casas-Tinto, 2020; Read, 2011; Read et al., 2009; Wirsching et al., 2016)). Among these mechanisms JNK pathway activation is a hallmark, classically associated to cancer stem-cell like properties, cancer initiating potential and glial proliferation (Kitanaka et al., 2013; Matsuda et al., 2012; Portela et al., 2019).

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The most common genetic lesions in GB patients include the Epidermal Growth Factor Receptor (EGFR) mutations, loss of PTEN (antagonist of PI3K), and the mutation of the catalytic activity domain of PI3K (Furnari et al., 2007; Louis et al., 2016; Wirsching et al., 2016). *Drosophila* model of GB is based on the constitutive activation of EGFR and PI3K pathways in glial cells. These mutations cause the transformation of glial cells, the development and progression of a GB, and associated neurodegeneration (Jarabo et al., 2021; Portela et al., 2019; Portela, Mitchell, & Casas-Tinto, 2020; Read, 2011; Read et al., 2009). Although *in vitro* and *in vivo* experiments suggest a positive correlation of EGFR and JNK activation with glioma grades (Kitanaka et al., 2013; J. Y. Li et al., 2008), there are EGFR-negative-glioblastoma samples with JNK activation (J. Y. Li et al., 2008).

Recent findings in *Drosophila* stablish the progressive chronology of the signalling pathways that mediate tumor growth and invasion. GB aggressiveness correlates with JNK pathway progressive activation (Portela, Mitchell, & Casas-Tinto, 2020). First, the tumor induces neurodegeneration, followed by an infiltration through the brain with ultra-long extended glial membrane protrusions known as cytonemes (mimicking mammals tumor microtubes, TMs), and GB cells proliferation (Casas-Tintó & Portela, 2019; Osswald et al., 2015; Portela, Mitchell, & Casas-Tinto, 2020). This glial network triggers cell-to-cell communication promoting neuron-glia signalling molecules exchange in benefit of JNK activity in GB cells, relevant for tumor invasion (Portela et al., 2019; Portela, Mitchell, & Casas-Tinto, 2020) (Jarabo et al., 2021).

GB cells deplete neuronal Wg/WNT through TMs from the surrounding neurons. GB-TMs accumulate Fz1 receptor, promoting WNT signalling in GB cells at expense of WNT signalling attenuation in neurons, that causes a progressive loss of synapses (Portela et al., 2019). Moreover, WNT signalling pathway has been implicated in gliomagenesis and stem-like GB cells properties (Kahlert et al., 2015). This signalling imbalance among GB cells and neurons mediates JNK activation in cancer cells, that leads to an upregulation of JNK target genes including matrix metalloproteases (MMPs) (Portela et al., 2019). MMPs mediate extracellular matrix (ECM) degradation and therefore, facilitate TMs infiltration (Portela et al., 2019). Thus, the expansion of TMs network promotes the communication among cells, maintaining a positive loop for Wg/WNT-JNK activity and TMs infiltration, neurodegeneration and glial cell proliferation (Portela et al., 2019) (Portela, Mitchell, & Casas-Tintó, 2020). Moreover, JNK signaling pathway is modulated by other mechanisms. *Drosophila* JNK ligand Egr is expressed in neurons under physiological conditions, but in GB samples there is a progressive increase of JNK pathway activation via Grnd receptor by a re-localization of the ligand from neurons to glial cells (Portela, Mitchell, & Casas-Tinto, 2020). Consistently with the tumor chronogram, the re-localization of Egr to glial cells coincides with the synapse loss, as a previous event to tumor infiltration and proliferation. More recently, it has been described that GB cells produce

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Impl2, an insulin pathway antagonist, as a mechanism to induce neuronal alterations including mitochondrial damage, contributing to neurodegeneration and tumor progression (Jarabo et al., 2021). This strategy is also mediated by JNK activity that regulates *Impl2* levels of expression in GB cells (Jarabo et al., 2021). Thus, GB cells require different strategies that converge into JNK signalling to further growth at expenses neighbouring neurons through TMs and, thereby, triggering neurodegeneration (Figure 2).

After surgical removal, radiotherapy and chemotherapy, the appearance of secondary tumours is frequent and less than 5% of the patients survive beyond 5 years (Gallego, 2015). Radiotherapy increased signalling communication among cancer cells through TMs that facilitate radiotherapy resistance (Osswald et al., 2015). Hence, TMs network is responsible of tumor aggressiveness but also to conventional therapy resistance and turns into a potential target to approach tumor malignancy (Osswald et al., 2015) . For example, Temozolomide (TMZ) is the most effective anti-glioma agent, however the administration doses is restricted to the limited patient survival that limits drug effect and patients can develop treatment resistance (Messaoudi et al., 2015; Stupp et al., 2005). In vitro cell culture experiments reveal that JNK pathway mediate TMZ resistance cytotoxicity by an increase of JNK phosphorylated levels (VO et al., 2014). Thus, JNK inhibitors emerge as potential candidates for glioblastoma pathogenesis and propose a therapeutic opportunity for TMZ administration (Matsuda et al., 2012; VO et al., 2014). *In vitro* and *in vivo* experiments show that JNK inhibitors prevent tumor formation and increase the survival rate (Matsuda et al., 2012). Similarly, Egr knockout experiments as well as Grnd knockout or Bsk dominant negative form in *Drosophila*, rescue tumor proliferation and invasiveness through the healthy brain (Portela, Mitchell, & Casas-Tinto, 2020).

JNK in neurodegenerative disorders

There are multiple stress stimuli that drive neurodegeneration, inducing programmed cell death, necrosis and autophagy (reviewed in Hou et al., 2019). Aging, accumulation of misfolded proteins, oxidative stress, inflammation and hypoxia are the classical stimuli that alter cell homeostasis and shift the balance into a stressful condition, where cells tend to degenerate (reviewed in Gan et al., 2018; Hou et al., 2019). JNK pathway has been extensively studied related to cell death by suppressing anti-apoptotic mechanisms, in favour of caspase apoptotic cascade (reviewed in (Dhanasekaran & Reddy, 2008)). Among the three JNK isoforms, JNK3 is the major isoform expressed in the CNS neurons and it contributes to neuronal cell degeneration (reviewed in Musi et al., 2020); Nakano et al., 2020). Additionally, JNK3 plays a role in synapse dysfunction, one of the first events in neurodegenerative and neurodevelopmental brain diseases (Sclip et al., 2014). Therefore, JNK3 has been proposed to

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be involved in neuronal cell death mechanisms in neurodegenerative disorders, adding a new promising target to approach CNS illnesses.

As an example, JNK activation is one of the hallmarks in Alzheimer´s disease (AD), and JNK3 phosphorylated levels correlate with the progression of the pathology (Bozyczko-Coyne et al., 2002; Gourmaud et al., 2015). AD is the most frequent neurodegenerative disorder, it is based on the aggregation of neurofibrillary tangles and Aβ peptides deposition in cortical and hippocampal neurons (reviewed in (Hepp Rehfeldt et al., 2020). Aβ-JNK mechanism mediate the reduction of anti-apoptotic Bcl-w genes expression, required for the apoptosis of cortical neurons that occur in AD progression (Yao et al., 2005). In addition, phosphorylated tau promotes tangles formation, and correlates with JNK enzyme activity (Yoshida et al., 2004). It is described that before early onset of the pathology, JNK signalling pathway is activated in the excitatory postsynaptic neuronal dendritic spines inducing synapse loss (Sclip et al., 2014). *In vitro* and *in vivo* JNK knockout experiments have reported a reduction in synapse loss, Aβ depositions and neuronal cell death (Hepp Rehfeldt et al., 2020; Sclip et al., 2014; Tiziana Borsello & Gianluigi Forloni, 2007). These evidences indicate that JNK signalling plays a central role in AD neurodegeneration, but also JNK emerges as a potential biomarker for early diagnosis and a potential target to prevent neuronal cell death (Hepp Rehfeldt et al., 2020).

In line with other synucleinopathies, JNK pathway signals also mediate neuronal cell death in Parkinson disease (PD). *In vitro* and *in vivo* PD models reveal the induction of JNK3 activation in dopaminergic neurons of the *substantia nigra* after the administration of neurotoxins (Choi et al., 2010). Similarly, *Drosophila* PD model show progressive neurodegeneration, and Bsk phosphorylation, supporting the conserved role of JNK in neurodegeneration (Yang et al., 2018). As well as JNK3 knockout experiments, Bsk dominant negative genetic construction in DA neurons rescues survival, neurodegeneration and locomotion impairment (Choi et al., 2010; Yang et al., 2018).

However, JNK signalling is not restricted to canonical cell death in neurodegeneration and participates in other features of neural tissues including axonal transport. For example, polyQ-htt induces JNK3 activity in Huntington disease (HD) models, leading to fast axonal transport inhibition through phosphorylation of kinesin-1 motor protein, that induces microtubule dissociation (Morfini et al., 2009). Additionally, kinase inhibitors reduce the extension of brain lesion area by blocking the JNK pathway, and confers neuroprotection (Perrin et al., 2009).

JNK in regeneration/repair after an injury in the CNS

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Several evidences support the importance of JNK signaling in response to nerve injuries in both degeneration and repair. In the injured axons, retrograde transport of JNK can alter somal transcription of the injury response molecules ATF3 and Hsp27, important for axonal outhgrowth (Lindwall & Kanje, 2005; Pathak et al., 2020). On the other hand, genetic or pharmacological inhibition of JNK signaling in multiple models of axonal injury delayed axonal degeneration (MacDonald et al., 2013; Syc-Mazurek & Libby, 2019), indicating that JNK is also required for axonal degeneration. Moreover, upon nerve injury of rat model, MAPK10/JNK3 inhibits axonal growth through the interaction with the Kluppel-like transcription factor 9 (KLF9) (Apara et al., 2017). Besides, JNK signaling activate members of the Bcl-2 family triggering apoptosis after injury or stress (Kim & Choi, 2010; Puthalakath et al., 2007; Tabas & Ron, 2011)

MAP3K is one of the first members of JNK pathway. It is a dual leucine zipper kinase (DLK), a conserved kinase with orthologues in mammals (MAP3K DLK), *Drosophila* (DLK/Wallenda) and *C. elegans* (DLK-1) (Jin et al., 2019). MAP3K is an important axon injury sensor (Valakh et al., 2015). DLK-JNK signaling contributes in multiple ways to axonal injury response signaling and axonal regeneration. DLK protein is present in axons, and protein levels are increased in response to axonal injury in *Drosophila* (Xiong et al., 2010; Xiong & Collins, 2012). JNK-dependent phosphorylation of DLK is required for the stabilization of DLK levels (Huntwork-Rodriguez et al., 2013). DLK regulates microtubule stability (Hirai et al., 2011; Simard-Bisson et al., 2017; Valakh et al., 2015), essential for axonal regeneration in spinal cord injury (Hellal et al., 2011). DLK overexpression has also been shown to be protective of *Drosophilia* motor neuron axons (Xiong & Collins, 2012). DLK is also an essential molecule for the injury-dependent activation of the retrograde transport of p-STAT3 to the cell body, necessary for the activation of the neuronal regenerative program in mice (Shin et al., 2012). Moreover, it has been demonstrated that in C. elegans DLK-1 is both necessary and sufficient for injury-induced autophagy activation, DLK-1 limits the levels of LIN-12 and NOTCH proteins, suggested to promote axon regeneration (Ko et al., 2020).

All the evidences summarized above demonstrate the importance of JNK signalling in injured axons however, JNK signalling activation also occurs in glial cells in response to injury. Different injury paradigms in *Drosophila* showed a consistent activation of AP-1 transcription in glial cells upon injury, which is downstream of JNK. Unknown molecules from axonal debris activate the engulfment receptor Draper which, in turn, regulates *draper* transcriptional upregulation via STAT92E (Doherty et al., 2014) and JNK pathway (MacDonald et al., 2013). Draper is a conserved receptor with orthologues in mammals (MEGF10) and *C. elegans* (CED-1), and it is required for engulfment in several cell types, including germ line, epithelial cells,

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microglia and astrocytes (Casas-Tintó et al., 2015; Colonna & Butovsky, 2017; Etchegaray et al., 2012; Morizawa et al., 2017).

In *Drosophila* and C. elegans, downregulation of JNK reduces axon regeneration and provokes axon debris accumulation following injury. In the injury context JNK also activates MMP-1 expression (Purice et al., 2017), which is required for glial cells to infiltrate in the injured tissue and remove cell debris via Draper. Glial-specific overexpression of *draper* is sufficient to rescue engulfment defects associated with loss of JNK signaling (MacDonald et al., 2013). In addition, knockdown of JNK pathway components blocks CED-1 mediated axon regeneration and axon debris removal (Chiu et al., 2018), this suggests a role for JNK in Drpr/CED-1-mediated axon regrowth.

Finally, JNK could also trigger CNS regeneration by promoting neuronal differentiation from Neural Stem Cells. So far, neurogenesis in mammals is restricted to two mayor regions, the sub-ependymal zone (SEZ) and the subgranular zone (SGZ) of the dentate gyrus, where adult Neural Stem Cells (NSCs) are present but the neuronal differentiation rate of NSCs is limited (X. Li et al., 2020). Therefore a promising strategy to boost CNS regeneration is to find candidates to promote neural differentiation from NCSs. Non canonical Wnt signaling such as the Wnt/JNK pathway has a positive effect on neuronal differentiation in cell culture and during development. (Blakely et al., 2013; Jang et al., 2015; Park et al., 2018). Moreover it has been recently shown that Wnt5a upregulates *miRNA200b-3p* expression through MAPK/JNK signaling, and *miRNA200b-3p* suppresses RhoA/Rock signaling required for neuronal differentiation. Thus, Wnt5a promotes NSC differentiation into neurons, and more remarkably, transplantation of NSCs overexpressing Wnt5a results in tissue repair and locomotor functional recovery in rats after spinal cord injury (X. Li et al., 2020).

Conclusions

JNK pathway is involved in multiple biological features describing a key role in the CNS. The complexity of this signalling pathway is demonstrated by the evidences of JNK having opposite functions depending on the tissue and the cellular environment. Hence, it is difficult to have a clear-cut understanding of the contributions of this kinase cascade to the cell physiology. However, here we review the most important roles of JNK in the CNS pathologies and as a potential pharmacological target to prevent its consequences. In this context, the CNS cells trigger a stress response increasing JNK levels that leads into a predominant cell death programme in neurodegenerative events, tumour aggressive properties in glioblastoma progression and neurodegeneration or promotion of axonal regeneration upon an injury. All the evidences here described, with the availability of JNK pathway conserved organism models

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such as *Drosophila melanogaster* or *C. elegans*, will contribute to decipher the multiple JNK activities and open promising clinical perspectives to treat CNS pathologies.

Figure legends

Figure 1. JNK pathway is conserved between mammals and flies. Upon internal and external stress stimuli ligands (ex. TNF/Egr) activate transmembrane receptors (ex. TNFαR/ Grnd) and initiates a cellular response based on a MAPK cascade phosphorylation. In mammals, different ligands (TNF, FasL, cytokines…) can trigger the signal path; while in *Drosophila* Eiger (Egr) is the TNF ligand that predominantly initiates the stress response via TNF receptors (Grindewal, Grnd, or Wengen, Wng). In mammals, there is MAPK path gene redundancy that is shown in this diagram comparing with flies. MAPKs are encoded by multiple genes in mammas, whereas in *Drosophila* one single gene is described for each enzyme. The cellular response converges in JNK/Bsk phosphorylation that triggers the expression of transcription factors as Jun/Jra and Fos/Jay, known as a AP-1/dAP-1 complex. Finally, AP1/dAP-1 modulates de transcriptional program of genes involved in a variety of biological activities. This pathway can be activated at other steps indicated with dotted lines in the diagram.

Figure 2. JNK pathway in CNS pathologies. A) JNK integrates a positive loop promoting tumour growth and neurodegeneration. GB cells extended a TMs network wrapping the surrounding neurons, promoting glia-neuron signalling communication. TMs filaments deplete neuronal Wg/WNT and Egr/TNF and re-localize Frizzled 1 and Grnd to activate JNK pathway in tumour cells. JNK activation leads on a MMPs transcription, required for tumour infiltration into the healthy tissue, this expands the TMs network, thereby, describing a positive feedback loop. As a result, neurons degenerate. Neurodegeneration is also reinforced by the JNK-Impl2-InR signal in neurons that alters mitochondrial metabolism and facilitates synapse loss and neuronal death. **B) Neuronal and glial JNK pathway mediates opposite roles upon CNS injury.** JNK activation in injured axons can promote axon degeneration by activating downstream molecules such as ATF3/Hsp27, KLF9 which inhibit axonal growth or members of the Bcl-2 family to trigger apoptosis. JNK activation in injured axons also promotes axonal growth through Wnd/MAP3K/DLK-1 phosphorylation which increases microtubule stability. JNK activation in glial cells upon injury is triggered by Draper and it is required for further Draper activation as well as for cells debris removal. JNK activates MMP-1, necessary for glial infiltration for cell debris clearance. This phagocytic response is necessary for axonal regeneration.

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