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REVIEW ARTICLE

THE CELL SURVIVAL FUNCTION OF JNK

Qing-Hua Wu[1,2,3], Zong-Hui Yuan[2], Xiu-Juan Zhang[4]✉

[1] College of Life Science, Yangtze University, Jingzhou, Hubei, China
[2] National Reference Laboratory of Veterinary Drug Residues (HZAU) and MAO Key Laboratory for Detection of Veterinary Drug Residues; MOA Laboratory of Risk Assessment for Quality and Safety of Livestock and Poultry Products, Huazhong Agricultural University, Wuhan, Hubei 430070, China
[3] Center for Basic and Applied Research, Faculty of Informatics and Management, University of Hradec Kralove, Hradec Kralove, Czech Republic
[4] College of Horticulture & Gardening, Yangtze University, Jingzhou, Hubei, China

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Summary

c-Jun N-terminal kinases (JNK) can be activated by multiple environmental stress, leading to varied and contradictory cellular response. JNK mediates cell apoptosis as well as cell survival and proliferation. JNK1 and JNK2 as the major members are able to perform similar and distinct biological functions. This review mainly discussed the mechanism of JNK cell survival function and the distinct roles of JNK1 and JNK2 in cell apoptosis and proliferation. Transient JNK activation may be important for mediating a survival response in TNF-treated cells and chronic JNK activation may contribute to apoptotic response. Other signal transduction pathways may also participate in its protective function. Abrogation of p38 MAPK pathway is assumed to induce pro-survival role. JNK suppresses apoptosis via phosphorylation of the pro-apoptotic Bcl-2 family protein BAD. Activated JNK inactivates suppressors of the apoptotic machinery, thereby "breaking the brake" on apoptosis.

Key words: JNK; apoptosis; cell survival; JNK1; JNK2

ABBREVIATIONS

JNK: c-Jun N-terminal kinases,
MAPK: the Mitogen-Activated Protein Kinase,
TNF-α: tumor necrosis factor-α,
MEFs: mouse embryonic fibroblasts,
TDP-43: DNA-binding protein-43,
CPF: pesticide chlorpyrifos,
EETs: poxyeicosatrienoic acid,
TPA: 12-O-tetradecanoylphorbol-13-acetate,
dpp: decapentaplegic,
wg: wingless.

✉ Yangtze University,
College of Horticulture & Gardening,
Jingzhou, Hubei, China
zxj510@aliyun.com
☎ +867168066262
+867168066262

INTRODUCTION

c-Jun N-terminal kinase (JNK) forms an important subgroup of the mitogen-activated protein kinase (MAPK) superfamily. JNK has three isoforms, both JNK1 and JNK2 are ubiquitously expressed, whereas JNK3 is expressed predominantly in the brain and,

to a lesser extent, in the heart and testis (Chang and Karin, 2001; Chen, 2012). JNK can be activated by various types of environmental stress, including osmotic shock, UV radiation, heat shock, oxidative stress, protein synthesis inhibitors, chemotherapeutic agents, and proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α) (Shen and Liu, 2006). Based on these types of stress, JNK is involved in controlling diverse cellular functions such as cell proliferation, differentiation and apoptosis.

It is well known that JNK plays an important role in cell pro-apoptosis. $JNK^{-/-}$ mouse embryonic fibro-blasts (MEFs) showed resistance to apoptosis in response to UV irradiation, DNA-alkylating agent methyl methanesulfonate, and translation inhibitor anisomycin (Tournier et al. 2000). Similarly, JNK activation is required for TNF-α-induced apoptosis in human hepatocarcinoma cells (Minero et al. 2013). In another study, the low-grade over expression of DNA-binding protein-43 (TDP-43) increases the level of phosphorylated JNK and the co-incubation with a JNK inhibitor, the expression of a dominant-negative JNK, or the expression of a dominant-negative c-Jun inhibited the TDP-43-induced death in NSC34 motor neuronal cells (Suzuki and Matsuoka, 2013). JNK pathway is also involved in isoflurane-induced apoptosis in the hippocampus of neonatal rats (Li et al. 2013). In a murine model of age-related macular degene-ration, JNK inhibition reduces apoptosis and neovascularization (Du et al. 2013). In addition, JNK might be critical mediators in a pesticide chlorpyrifos (CPF)-induced neuronal apoptosis by both generating ROS and up-regulating COX-2 (Ki et al. 2013). All these studies demonstrated that JNK is involved in cell apoptosis.

JNK could be activated by multiple and diverse stimuli leading to varied and seemingly contradictory cellular response. Different researches have concluded that JNK has a Janus face, or called "double edged sword" and regulates cell survival process (Bode and Dong, 2007; Liu and Lin, 2005). It appears that sustained activation of JNK is associated with apoptosis, whereas the acute and transient activation of JNK is involved in cell proliferation or survival pathway (Chen and Tan, 2000; Ventura et al. 2006; Dhanasekaran and Reddy, 2008). Other studies state that the different JNK functions might occur through the specific substrate choice or might be related to temporal aspects (Bode and Dong, 2007). Moreover, JNK1 and JNK2 seem to have opposite roles in cell apoptosis (Conze et al. 2002). For example, JNK1 and JNK2 can oppositely regulate p53 in signaling linked to apoptosis triggered an altered fibronectin matrix (Tafolla et al. 2005).

Several reviews have well summarized the pro-apoptotic function of JNK (Dhanasekaran and Reddy, 2008; Chen, 2012; Lin, 2002). Here we are more interested in JNK's cell survival function. In this review, we will attempt to summarize the cell survival function of JNK and discuss the underlying mechanisms. Moreover, the distinct functions of JNK1 and JNK2 with recent discoveries on the roles of apoptosis and cancer development will be discussed as well. This work may help to further understand the cell survival roles of JNK and shed some light on the pathogenesis of cancer.

ROLE OF JNK IN CELL SURVIVAL

Initial biochemical studies show that JNK is a mediator of apoptosis. However, subsequent studies reveal that JNK could also be anti-apoptotic or could regulate cell survival (Lenczowski et al. 1997; Lin and Dibling, 2002).

To determine the combined roles of JNK1/2 in the process of proliferation, mice lacking both loci *Jnk1* and *Jnk2* were generated (Sabapathy et al. 1999). *Jnk1/Jnk2* double mutants (i.e. $Jnk1^{-/-}$, $Jnk2^{-/-}$) could cause embryonic death and exhibit failure of neural tube closure. Similarly, Kuan et al. (1999) observed that mice deficient in *Jnk1*, *Jnk2*, *Jnk3*, and *Jnk1/3*, *Jnk2/3* double mutants all survived normally. Moreover, compound mutants lacking *Jnk1* and *Jnk2* genes were embryo-lethal and had severe apoptotic dysregulation in brain. In addition, *JNK1* was demonstrated to directly phosphorylate with Bcl-2 *in vitro*, co-localized with Bcl-2, and collaborated with Bcl-2 to mediate prolonged cell survival in the absence of IL-3 or following various stress applications (Deng et al. 2001). Recently, bortezomib was shown to induce up-regulation of the pro-survival and pro-death ER stress molecules BIP and CHOP and activated JNK, resulting in Bcl-2 phosphorylation and induction of autophagy (Granato et al. 2013). JNK and autophagy activation played a pro-survival role in this setting, and their inhibition increased the bortezomib cytotoxic effect and PARP cleavage in PEL cells.

JNK group of MAPK is important for survival of macrophages in response to cytokine, CSF-1 (Himes et al. 2006). CSF-1 is critical for survival of mature non-dividing macrophages. JNK inhibition could result in decreased expression of CSF-1R (*c-fms*) and Bcl-xL mRNA in mature macrophages and repressed CSF-1-dependent differentiation of bone marrow cells to macrophages. Inhibition of JNK disrupted transcription factor PU.1 binding to an element in the *c-fms* gene promoter and decreased promoter activity. Lamb et al. (2003) demonstrated that JNK-mediated survival signaling was mediated by JunD. JNK/JunD pathway can collaborate with NF-κB to increase anti-apoptotic gene cIAP-2 express. In the absence of activated ND-κB, the JNK pathway mediated an apoptotic response.

In another study, epoxyeicosatrienoic acid (EETs) was shown to stimulate pulmonary artery endothelial cells proliferation and angiogenesis, as well as protect the cells from apoptosis, via the JNK/c-Jun pathway (Ma et al. 2012). In their study, treatment with EETs promoted cell proliferation and cell cycle transition from G0/G1 phase to S phase and stimulated the tube formation *in vitro*. All these effects were reversed after blocking JNK with SP600125 (a JNK inhibitor) or JNK1/2 siRNA.

In cancer studies, JNK1 was a crucial suppressor of skin tumor development (She et al, 2002). This result cannot be called "cell survival", but JNK could inhibit the tumor cell development to 'survive' humans or animals. JNK1-deficient ($Jnk1^{-/-}$) mice were more susceptible to the tumor promoter, 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced skin tumor development than wild-type mice. The rate of tumor development in $Jnk1^{-/-}$ mice was significantly more rapid than that observed in wild-type mice.

THE MECHANISM OF CELL SURVIVAL

The role of JNK in apoptosis is highly dependent on the cellular context, such as the cell type, the nature of the death stimuli, the duration of JNK activation and the activity of other signaling pathways (Lin, 2003). Currently, the precise molecular mechanism of cell survival function of JNK is not entirely clear. Nevertheless, several potential mechanisms are proposed from different studies.

Lamb et al. (2003) have proposed two potential mechanisms for the different roles of JNK in apoptotic signaling. One mechanism is represented by the time course of JNK activation. Transient JNK activation may be important for mediating a survival response in TNF-treated cells and that chronic JNK activation may contribute to apoptotic response. A second mechanism of JNK is that the biological consequence of JNK function may depend upon the activation state of other signal pathways. JNK may cooperate with other signaling pathways to mediate cell survival (e.g., NF-κB and AKT). Similarly, Ventura et al. (2006) also showed that the time course of JNK signaling can influence the biological response to JNK activation. In their study, the early transient phase of JNK activation (< 1 h) can signal cell survival, while the later and more sustained phase of JNK activation (1 - 6 h) can mediate pro-apoptotic signaling. The authors supposed that the requirement of early JNK activation for the survival response was a consequence of the need for the expression of anti-apoptotic genes at early time during the response to an inducer of apoptosis. Other ubiquitin ligases, for example AIP4/Itch, or non-transcriptional responses (such as ubiquitin ligase cIAP2) may also contribute to the cell survival response (Lamb et al. 2003; Gao et al. 2004).

In another study, JNK was supposed to suppress apoptosis via phosphorylation of the pro-apoptotic Bcl-2 family protein BAD (Yu et al. 2004). IL-3 is a key survival factor that suppresses the occurrence of apoptosis, once withdrawn IL-3 can induce cell apoptosis. JNK is required for IL-3-mediated cell survival through phosphorylation and inactivation of the proapoptotic Bcl-2 family protein BAD. JNK could phosphorylate BAD at Threonine 201, thereby inhibiting BAD association with the anti-apoptotic molecular Bcl-xL. IL-3 induces BAD phosphorylation at Threonine 201, and replacement of Threonine 201 by Alanine generates a BAD mutant, which could promote IL-3 withdraw-induced apoptosis.

JNK was shown to have a unique pro-survival role in B-lymphoma model (Gururajan et al. 2005). Survival signals provided by CD40 and IL-10 together reversed the growth inhibition induced by the JNK inhibitor. Moreover, JNK may act via c-Myc and Egr-1, which were shown to be important for B-lymphoma survival and growth. Targeting JNK may have some important therapeutic implications in the treatment of B-lymphomas. Recently, Svensson et al. (2011) have shown that both JNK and p38 MAPK pathways

possess anti-apoptotic functions in the microglial cell line BV-2 during LPS induced activation. They proposed that the pro-survival role of JNK is possible due to its abrogation of a potentially apoptotic signal mediated by p38 MAPK pathway.

JNK could mediate cell apoptosis, which is an important process for tumor suppression. However, JNK has also been implicated in the mali-gnant transformation and tumorigenesis of cells. As for the potential mechanism of the contradictory function, Chen (2012) made an explanation that a compensatory proliferation of neighboring cells might be triggered by the apoptotic, stress cells. In other words, the compensatory growth might be an essential linker to bridge apoptosis and carcinogenesis. This hypothesis was also supported by Ryoo et al. (2004). Apoptotic cells express the secreted factors wingless (wg) and decapentaplegic (dpp). In their study (Ryoo et al. 2004), when cells undergoing apoptosis were kept alive with the caspase inhibitor p35, excessive nonautonomous cell proliferation was observed. Drosophila inhibitor of apoptosis protein DIAP1 antagonist reaper and hid can activate the JNK pathway and this pathway is required for inducing wg and cell proliferation.

An important hypothesis of "Breaks the brake" was proposed by Lin (2002) to explain the mechanism of JNK in apoptosis regulation. JNK may be a modulator rather than an intrinsic component of the apoptotic machinery. Thus, JNK activation facilitates but does not induce apoptosis. They hypothesize that activated JNK inactivates suppressors of the apoptotic machinery, thereby "breaking the brake" on apoptosis. It is shown that TNF-α is able to induce apoptosis in cells sensitive to it (Tang et al. 2002). The distinct role of JNK activation in TNF-α induced apoptosis could be explained using this model. While caspase activation initiates and executes apoptosis, prolonged JNK activation promotes apoptosis by inactivating suppressors of the mitochondrial-dependent death pathway. Activation of NF-κB by TNF-α blocks caspase activation and prevents prolonged JNK activation, thereby inhibiting TNF-α-induced apoptosis.

THE DISTINCT ROLES OF JNK1 AND JNK2 IN APOPTOSIS

Both JNK1 and JNK2 share the same substrates, including activating transcription factor 2 and c-Jun transcription factors, and were assumed to complement each other and mediate the same or similar biological functions (Chen et al. 2002; Liu et al. 2004). However, increasing studies report that there are distinct functions between JNK1 and JNK2, although the underlying mechanism of the different functions is still unclear.

JNK1, but not JNK2 is essential for tumor necrosis factor-alpha (TNF-α)-induced c-Jun kinase activation, c-Jun expression, and apoptosis. In addition, JNK2 could interfere with JNK1 activation via its "futile" phosphorylation by upstream kinases (Liu et al. 2004). Conze et al. (2002) observed the distinct roles for JNK1 and JNK2 in $CD8^+$ T cell activation. The absence of JNK2 causes increased IL-2 production and proliferation of $CD8^+$ T cells. In contrast, JNK1-deficient $CD8^+$ T cells are unable to undergo antigen-stimulated expansion *in vitro*, even in the presence of exogenous IL-2. Chen et al. (2002) have shown that 7,12-dimethylbenz(a)anthracene/12-O-tetradecanoylphorbol-13-acetate-13-acetate-induced tumor development is suppressed in *Jnk2* knockout mice but enhanced in *Jnk1* knockout mice. Sabapathy et al. (2004) demonstrated the distinct roles for JNK1 and JNK2 in regulating JNK activity and c-Jun-dependent cell proliferation. JNK2 deficiency results in elevated c-Jun phosphorylation and stability, whereas the absence of JNK1 reduces c-Jun phosphorylation and stability. $Jnk2^{-/-}$ fibroblasts exit G1 and enter S phase earlier than wild-type counterparts, while $Jnk1^{-/-}$ cells show the inverse phenotype. Moreover, $Jnk2^{-/-}$ erythroblasts also exhibit a proliferate advantage.

Tafolla et al. (2005) reported that the apoptotic mechanism triggered by an altered fibronectin (FN) matrix is propagated by decreases in focal adhesion kinase (FAK) phosphorylation that is linked to increased phosphorylation of JNK and to decreased levels of p53, which is oppositely relegated by JNK1 and JNK2. When JNK1 expression was abrogated with two different antisense oligonucleotides, p53 levels increased to a greater extent than in control cells or empty vector. However, abrogating JNK2 expression with antisense oligonucleotides resulted in a complete or nearly complete early reduction in p53 protein level.

JNK1 and JNK2 seem to differ substantially in the ability to interact with c-Jun. c-Jun is important for efficient transition of the G1-S phase of the cell cycle (Bode and Dong, 2007). Absence of JNK1,

the positive regulator of c-Jun, leads to decreased fibroblast proliferation. In contrast, JNK2 deficiency leads to reduced c-Jun degradation, thereby augmenting c-Jun levels and cellular proliferation (Sabapathy and Wagner, 2004). Their results show that JNK2, in contrast to JNK1, is a negative regulator of cellular proliferation in multiple cell types. Similarly, in another study, *Jnk2*$^{-/-}$ fibroblasts showed a slightly more rapidly proliferation in culture than did wild-type fibroblasts. However, the saturation density of WT and *Jnk2*$^{-/-}$ MEF was similar. In contrast, *Jnk1*$^{-/-}$ fibroblasts proliferated more slowly than did WT cells and they reached a lower saturation density (Tournier et al. 2000). Their results imply that JNK1, rather than JNK2, may be more important for proliferation and also implicating JNK1 as a positive regulator of c-Jun.

CONCLUSION

Depending on cell types, the nature of the apoptosis stimulus, the duration of its activation, and on the activity of other signaling pathways, JNK may display different, even opposite, functions. Currently, increasing studies have shown that JNK has cell survival function. However, the loss-of-function studies are unable to reveal whether JNK is directly or indirectly involved in cell survival and how JNK promotes cell survival. Moreover, most of the function studies of JNK1/2 are performed *in vitro*. Thus, further studies are needed to examine how JNK1 and JNK2 are differently regulated *in vivo*. Importantly, we need to understand that cancer cells can also utilize JNK anti-apoptotic function to protect from cell apoptosis. JNK is a potential target in cancer therapy.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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