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RECEIVED 16 July 2024

ACCEPTED 24 September 2024

PUBLISHED 07 October 2024

CITATION

Enomoto A, Fukasawa T and Yoshizaki A (2024) Hyperthermia-mediated cell death via deregulation of extracellular signal-regulated kinase and c-Jun NH₂-terminal kinase signaling. *Front. Cell. Death* 3:1465506. doi: 10.3389/fceld.2024.1465506

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Hyperthermia-mediated cell death via deregulation of extracellular signal-regulated kinase and c-Jun NH₂-terminal kinase signaling

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Hyperthermia is a promising anticancer treatment that induces heat stress, thereby stimulating various signal transduction pathways to maintain cellular homeostasis. Mitogen-activated protein kinases (MAPKs) associate various extracellular stimuli with cytoplasmic and nuclear mediators through a three-tiered cascade of kinases, including MAPKs, MAP2Ks, and MAP3Ks. In mammals, three major groups of MAPKs have been characterized: extracellular signal-regulated protein kinases (ERK1/2), p38 MAPKs (α , β , γ , and δ), and c-Jun NH₂-terminal kinases (JNK1/2/3). Each group of MAPKs is activated by heat and exhibits distinct biological functions. Recent studies have indicated that in hyperthermia, MAPK signaling pathways regulate cell survival and death in unique ways. This review offers a concise overview of the MAPK signaling pathway, specifically ERK and JNK, focusing on their relevance in cancer, interplay with heat shock proteins or phosphatases, and current understanding of the MAPK signaling pathway in hyperthermia.

KEYWORDS

MAPK, signal transduction, hyperthermia, heat shock proteins, phosphatases, cell death

1 Introduction

Hyperthermia is a treatment that raises the temperature of lesions with electromagnetic waves from outside the body and often used in combination with radiotherapy or chemotherapy. In most hyperthermia treatments, the temperature is maintained over 42.5°C in order to kill cancer cells. It increases cell temperature and induces various biochemical changes, such as reactive oxygen species (ROS) generation, an increase in intracellular calcium ion concentration, and protein degradation (Roti, 2008; Hou et al.,

Abbreviations: ROS, reactive oxygen species; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; JNK, c-Jun NH₂-terminal kinases; MAP2K; MAPK kinase; MEK, mitogen-activated ERK kinase; MKK, MAP kinase kinase; MAP3K, MAPKK kinase; RAF, rapidly accelerated fibrosarcoma; ASK, apoptosis signal regulating kinase; MEKK, mitogen-activated ERK kinase kinase; MLK, mixed lineage kinase; TGF- β , transforming growth factor- β ; NF- κ B, nuclear factor kappa B; HSP, Heat shock protein; DUSP, dual specificity phosphatase.

2014). Hyperthermia-induced protein denaturation, aggregation, and degradation significantly disrupt cellular homeostasis (Ahmed et al., 2020). Cellular proteins begin to denature above 42.5°C. The mitogen-activated protein kinase (MAPK) signal transduction pathway is conserved in eukaryotic cells (Chang and Karin, 2001). MAPK signaling pathways play a crucial role in the response of cells to various extracellular stimuli, affecting cell proliferation, differentiation, survival, and death (Lavoie et al., 2020; Zeke et al., 2016; Mlakar et al., 2021). Although studies have reported heat-induced activation of the MAPK signaling pathways (Ng and Bogoyevitch, 2000; Jin et al., 2018; Liu et al., 2022), the regulatory mechanisms involved in MAPK signaling remain unclear. This review aims to explore the contribution of MAPK signal transduction to hyperthermic cell death.

2 MAPK signaling

MAPK signaling pathways mediate cellular responses to various extracellular stimuli, including growth factors and environmental stresses (Chang and Karin, 2001). The MAPK signaling pathway consists of a three-kinase cascade, which includes MAPKs (extracellular signal-regulated kinase (ERK), p38, and c-Jun NH₂-terminal kinases (JNK), MAPK kinases (MAP2Ks; mitogen-activated ERK kinase (MEK) and MAP kinase kinase (MKK)), and MAPKK kinases (MAP3Ks; e.g., rapidly accelerated fibrosarcoma (RAF), mitogen-activated ERK kinase kinase (MEKK), transforming growth factor- β -activated kinase 1 (TAK1), apoptosis signal-regulating kinase 1 (ASK1), and mixed lineage kinase (MLK). MAP3Ks phosphorylate and activate MAP2Ks, thereby phosphorylating MAPKs. Biochemical and genetic analyses indicate that MAP3Ks associate various extracellular stimuli with cytoplasmic and nuclear effectors by activating downstream MAPK signaling pathways (Peterson et al., 2022). Twenty-one MAP3Ks have been identified to activate the known MAP2Ks. Upstream of the MAP3Ks, the signaling molecules involve kinases, adaptors, and receptors, which connect the pathway to specific stimuli (Chang and Karin, 2001) (Figure 1A).

RAS is a type of small GTP-binding protein and interacts with the RAF family. At the cell surface, the activation of the RAS-RAF-MEK-ERK1/2 signaling pathway is initiated by ligand binding to receptor tyrosine kinases (Simanshu and Morrison, 2022; Bahar et al., 2023). RAF1 is associated with oncogenesis and plays a crucial role in cell growth and development (Huang et al., 2017; Wang et al., 2023; Tran et al., 2021). RAF phosphorylates and activates MEK1/2, which can then activate ERK1/2 to phosphorylate both cytoplasmic and nuclear targets. The ERK1/2 cascade is primarily activated by growth factors, cytokines, agonists of tyrosine kinase-encoded receptors, and G protein-coupled receptors that induce mitogenesis or differentiation (Lavoie et al., 2020). In contrast, the JNK and p38 cascades are predominantly activated by pro-inflammatory cytokines, endoplasmic reticulum stress, or extracellular stress (Zeke et al., 2016; Mlakar et al., 2021; Chen et al., 2021). The MAP3Ks of the JNK pathway include sterile 20 (Ste20)/Ste11/Ste7 (STE) family kinases, such as ASK1, and tyrosine kinase-like (TLK) family members, such as MLKs. The primary MAP2Ks of the JNK cascade are MKK4/stress-activated protein

kinase (SAPK)/ERK kinase (SEK1) or MKK7 (Haeusgen et al., 2011; Park et al., 2019). ASK1 activates two different subgroups, the SEK1-JNK and MKK3/6-p38 pathways, and plays crucial roles in the induction of apoptosis (Hattori et al., 2009; Ryuno et al., 2017; Ogier et al., 2020). TAK1 originally associated with transforming growth factor- β (TGF- β)-mediated MAPK activation, is also activated by various cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF- α) (Sakurai, 2012; Xu and Lei, 2021). Subsequently, the activated TAK1 phosphorylates inhibitors of nuclear factor- κ B (I κ B) kinase (IKK) and MKKs (MKK3/6, MKK4/7), resulting in the activation of nuclear factor kappa B (NF- κ B) and JNK (Xu and Lei, 2021). MLK3 plays a role in cancer cell survival, migration, drug resistance, cell death, and tumor immunity (Kumar et al., 2021). Additionally, it induces the activation of the JNK and ERK signaling pathways. Oxidative stress-mediated B-Raf-MEK-ERK pathway activation results in a positive feedback loop, where ROS facilitates the ERK1/2-dependent phosphorylation of MLK3 (Schroyer et al., 2018).

3 MAPK signaling pathway in cancer

MAPK signaling pathways play crucial roles in tumor growth, metastasis, and invasion (Braicu et al., 2019). Specifically, the RAS-RAF-MEK1/2-ERK1/2 pathway has been predominant in cancer research (Tran et al., 2021; Bahar et al., 2023). Mutations in RAS and B-Raf proto-oncogene, serine/threonine kinase (BRAF) that dysregulate the MAPK signaling pathway are predominantly associated with human malignancies. RAS is extremely prevalent, with mutations detected in approximately 30% of all tumors (Fernández-Medarde and Santos, 2011). Although RAS activity varies across various cancer types, the upregulation of RAS activity results in the dysregulation of downstream protein kinase activities. RAF mutations, specifically in BRAF V600E, are frequently observed in melanoma and other cancers (Dillon et al., 2021). RAF1 alterations are observed in 2.3% of The Cancer Genome Atlas (TCGA) PanCancer Atlas samples (Cerami et al., 2012; Gao et al., 2013). Several BRAF inhibitors such as Vemurafenib were approved and showed significant benefits, but ineffectiveness was observed after long-term treatment. The MEK1/2 phosphorylation rates in colon cancer, villous adenoma, and tubular adenoma were 76, 40, and 30%, respectively, whereas in normal colonic mucosal cells, the MEK phosphorylation was merely detectable (Lee et al., 2004). Cobimetinib (GDC-0973) is an effective and highly selective allosteric MEK1/2 inhibitor and showed a good efficacy in BRAF and KRAS mutant cell lines and in BRAFV600E/K-mutant patients (Ribas et al., 2014; Amaral et al., 2016). Increased ERK1/2 activation is evident across various human cancer types, including ovarian, colon, breast, and lung cancer (Timofeev et al., 2024). In addition, the constitutive activation of the RAS/RAF/MAPK pathway contributes to tumorigenesis by inhibiting Caspase-9 through MAPK-dependent phosphorylation (Roh et al., 2014).

TAK1 plays a crucial role in regulating immune responses and cell survival through the NF- κ B and JNK signaling pathways (Inokuchi et al., 2010). Because TAK1 downstream molecules (NF- κ B and JNK) are involved in cancer cell survival and apoptosis, TAK1 regulates tumor initiation, proliferation, and

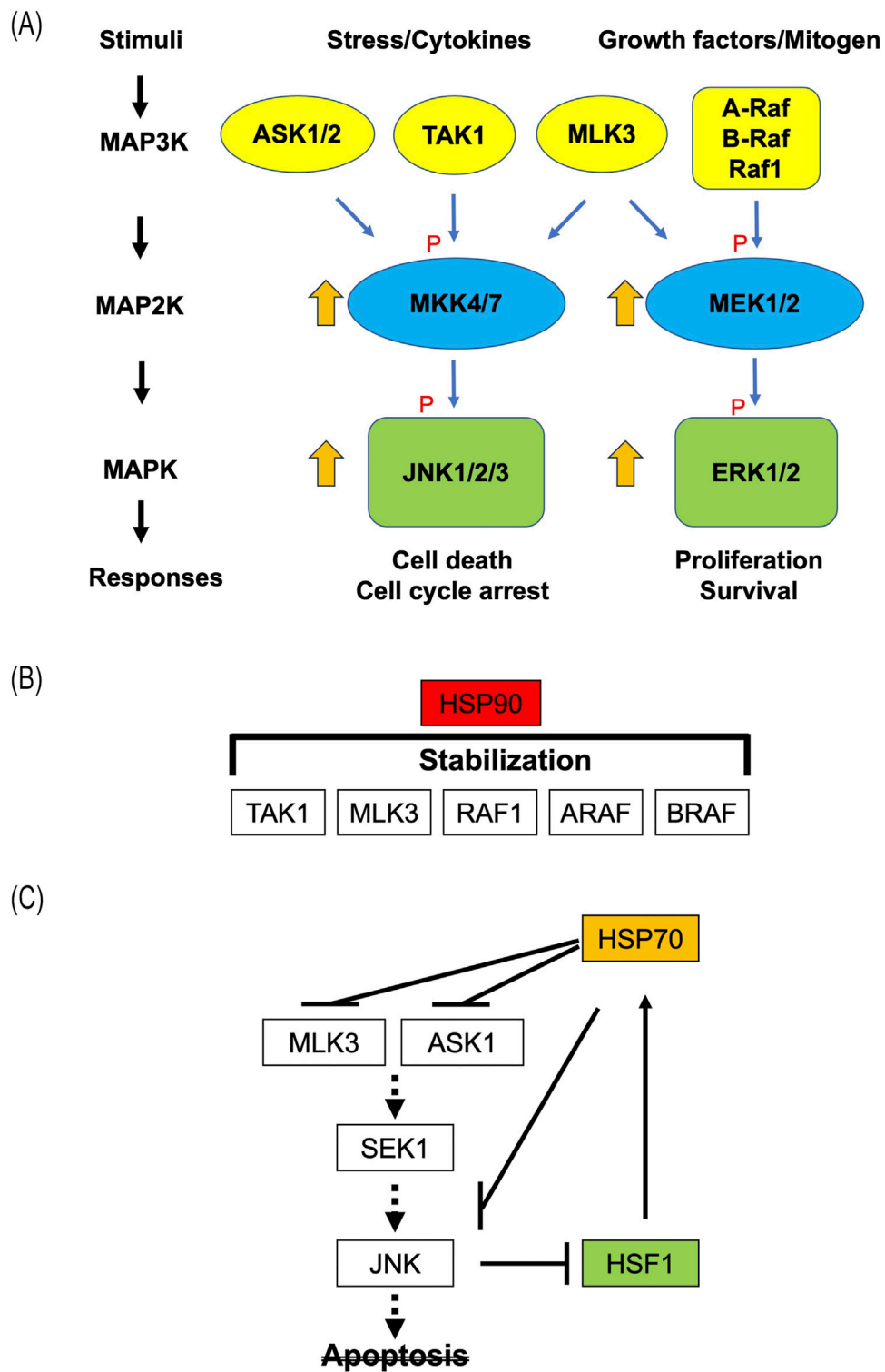


FIGURE 1
(A) Schematic representation of JNK and ERK pathways in MAPK signaling. Upon external stimulation, the three-tiered kinase modules comprising MAP3Ks, MAP2Ks, and MAPKs are activated through sequential protein phosphorylation. The majority of JNK and ERK signaling pathways are activated by the mitogen-activated protein-3 kinase (MAP3K) members, such as rapidly accelerated fibrosarcoma 1 (RAF1), apoptosis signal-regulating kinase 1 (ASK1), mixed lineage kinase 3 (MLK3), and transforming growth factor- β -activated kinase 1 (TAK1). The MAP3K cascades are involved in the regulation of cell growth and apoptosis. Multiple MAP3Ks can activate both JNK and ERK pathways. P, phosphorylation. **(B)** Roles of HSPs in regulation of MAPK signaling pathway. The stability of client proteins, including RAF1, ARAF, BRAF, TAK1 and MLK3, is influenced by HSP90 binding. **(C)** Modification of the JNK signaling pathway by HSP70. HSP70 prevents SEK1 activation through an interaction with ASK1. Binding of HSP70 to JNK prevents its phosphorylation by SEK1. JNK phosphorylates HSF-1 and suppresses its transcriptional activity. HSP, heat shock protein; HSF, heat shock transcription factor.

metastasis either as a promoter or suppressor, based on specific receptors and cell types (Cai et al., 2014). Overexpression and hyperactivation of TAK1 are associated with various cancers (Lin et al., 2015; Mukhopadhyay and Lee, 2020; Teramachi et al., 2021). Inhibition of TAK1 activity resulted in reduced cell proliferation, invasion, and apoptosis induction owing to abrogation of NF- κ B activation (Lin et al., 2015; Yang et al., 2017).

ASK1 facilitates ROS-induced and endoplasmic reticulum (ER)-mediated apoptosis (Ryuno et al., 2017). Reduced expression or activity of ASK1 has been observed in various cancers, including HCC and breast cancer (Jiang et al., 2016; Yin et al., 2017). However, increased ASK1 expression and activity facilitate cancer cell motility and proliferation in oral squamous cell carcinoma, ovarian, and pancreatic cancer (Luo et al., 2016; Chen et al., 2024). Recent report demonstrates that the deubiquitinase OTUD1-based aggresomes recruit ASK1 via protein-protein interactions, which in turn stabilize ASK1 and activate the downstream JNK signaling pathway for ovarian cancer stem cell maintenance (Chen et al., 2024).

MLK3 has been implicated in the regulation of tumor cell proliferation, differentiation, migration, invasion, and apoptosis (Ma et al., 2019). MLK3 expression is upregulated in hepatocellular carcinoma, and MLK3 blocking suppresses cancer progression (Ke et al., 2024). MLK3 directly binds to epidermal growth factor receptor kinase substrate 8 (EPS8) and regulates the cellular location of EPS8, suggesting that MLK3 promotes the migration and invasion by remodeling the actin cytoskeleton (Zhu et al., 2021). Knockdown of MLK3 expression reduces the breast cancer cell invasion by reducing MMP expression (MMP-1 and -9) (Rattanasinchai et al., 2017). The MLK3 kinase activity was higher in triple-negative (TNBC) than in hormone receptor-positive human breast tumors, and the knockdown of MLK3 or MLK3 inhibitors, CEP-1347 and URM-099, attenuated tumorigenesis of TNBC cell line and Patient-Derived xenografts (Nair et al., 2023).

Previously, JNK was conceived as an apoptosis driver for cell death, implying its potential as a tumor suppressor, as demonstrated in breast and pancreatic cancers (Cellurale et al., 2012). However, emerging evidence indicates that JNK has a Janus face that regulates both cell apoptosis and survival (Yan et al., 2024). JNK1 facilitates cell survival, whereas JNK2 mediates apoptosis and death (Arbour et al., 2002; Recio-Boiles et al., 2016). Additionally, JNK facilitates cell survival under adverse conditions, including low oxygen levels, by eliminating dysfunctional cellular components (Tam et al., 2019; Wu et al., 2019). Moreover, JNK-mediated pro-survival autophagy facilitates cancer cell resistance to chemotherapy (Huang et al., 2017). The JNK protein appears to be involved in both tumor promotion and inhibition based on stimuli, cell and tissue type, and isoform.

4 Role of heat shock proteins in regulation of MAPK signaling

Cells respond to heat by induction of heat shock proteins (HSPs) (Singh and Hasday, 2013). HSPs function primarily as molecular chaperones. This chaperone activity is diverse and includes facilitating the conformational maturation of its client proteins and regulating client protein location and translocation within the cell.

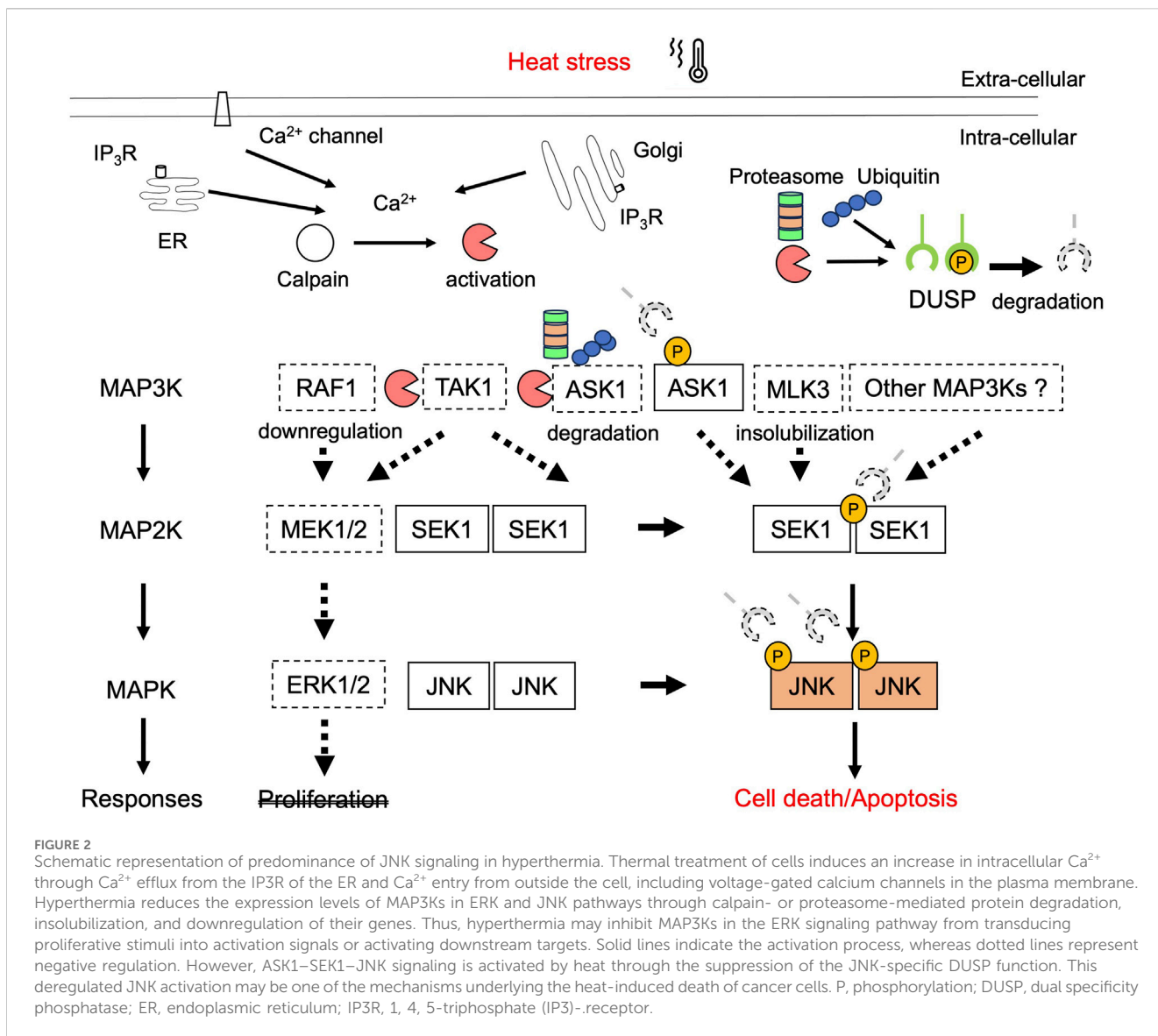
The primary proteins within the HSP family (Hsp70 and Hsp90) have numerous sets of protein clients and play crucial roles in the regulation of cell protein physiology (Streicher, 2019). In terms of cellular response to heat, previous other reports show a correlation between HSPs expression and activation of MAPKs (Hao et al., 2018; Liu et al., 2022).

HSP90, which is evolutionarily conserved, is anti-apoptotic and plays a crucial role in the folding, stabilization, activation, function, aggregation, and proteolytic degradation of several client oncoproteins (Schopf et al., 2017). Moreover, HSP90 is of considerable interest in the search for new therapeutic cancer targets, since most HSP90 client proteins are oncogenic proteins and protein kinases that regulate cell survival, proliferation, invasion, metastasis, and angiogenesis (Birbo et al., 2021). The clientele includes various MAPK-related kinases, including BRAF, CRAF, TAK1, and MLK3 (Liu et al., 2008; Rattanasinchai and Gallo, 2016; Roberts et al., 2021; García-Alonso et al., 2022) (Figure 1B). Suppression of HSP90 expression can result in the simultaneous co-inhibition of various client proteins, thereby affecting multiple signaling pathways (Antolin et al., 2021). For example, the HSP90 inhibitor 17-AAG suppresses ERK signaling in the majority of cell lines because it targets C-RAF, active BRAF, and most of the mutant forms of BRAF (García-Alonso et al., 2022). Consequently, inhibition of HSP90 antagonizes the characteristic pathological features of cancerous cells, including self-sufficiency in growth signals, non-responsiveness to growth-suppressive signals, evasion of apoptosis, angiogenesis, invasiveness, and metastasis (Birbo et al., 2021).

HSP70 is involved in regulating various physiological processes, including stress responses and apoptosis. Protective HSP70 expression was associated with the activation of the MAPK signaling pathway (Zhang et al., 2020). ERK-mediated induction of HSP70 may play a crucial role in the inhibition of apoptosis (Lee et al., 2015). Inhibition of HSP70 enhanced heat-induced JNK activation and cleavage of caspase-3 (Hao et al., 2018). There is a clear correlation between the dependence of apoptosis on the activation of JNK and the suppression of apoptosis through elevated Hsp72 expression (Park et al., 2001). Additionally, Hsp70 has been demonstrated to suppress JNK activation by specifically associating with JNK and preventing SEK1-mediated phosphorylation (Gabai et al., 1998) (Figure 1C). Moreover, HSP72 inhibits ASK1 activity by directly interacting with it (Park et al., 2002). The transcriptional activation of HSP genes is regulated by heat shock factors (HSFs). Post-translational modifications are crucial for complete HSF1 activation. Phosphorylation is the most extensively studied modification, with HSF1 undergoing both stimulatory and inhibitory phosphorylation (Dai, 2018). JNK phosphorylates HSF1 at Ser363, resulting in its inhibition (Dai et al., 2000). Additionally, HSF1 reciprocally prevents JNK activation (Su et al., 2016), indicating mutual suppression of JNK and HSF1.

5 MAPK signaling pathway in hyperthermia

Hyperthermia stimulates the release of inflammatory and growth factors including interleukin (IL)-1 β , IL-6, vascular



endothelial growth factor (VEGF), and tumor necrosis factor alpha (TNF- α) (Katschinski et al., 1999). These cytokines and growth factors stimulates activation of MAPK activators such as RAS. Hyperthermia activates multiple MAPK signaling pathways, including ERK, p38, and JNK (Ng and Bogoyevitch, 2000; Dorion and Landry, 2002; Jin et al., 2018; Liu et al., 2022). In numerous cell types, ERK1/2 activation facilitates cell survival, including during heat shock. For example, mild heat treatment at 42 °C induced ERK1/2 activation, which was inhibited by the MEK-specific inhibitor PD98059, thereby increasing the loss of cell viability (Ng and Bogoyevitch, 2000). Intense heat stress at or above 43 °C induces the dephosphorylation of ERK1/2 and B-cell lymphoma 2 (Bcl-2) and subsequent apoptosis through superoxide production (Li et al., 2017). In contrast, the JNK and p38 MAPK signaling pathways are often associated with pro-apoptotic effects. Dominant-negative JNK prevents heat-induced cell death and Bcl-2-associated X protein (Bax) translocation to mitochondria (Stankiewicz et al., 2005). SB2035800, an inhibitor of p38,

reduces heat-induced ROS accumulation and apoptosis (Li et al., 2018). Hyperthermia reduces the invasion of C6 glioma cells by stimulating TNF- α signaling to activate apoptosis, enhancing p38 MAPK expression, and inhibiting the NF- κ B signaling pathway in C6 rat glioma cells (Wang et al., 2012). Under mild hyperthermia, the transient activation of JNK and p38 results in cell differentiation rather than apoptosis (Nagata and Todokoro, 1999).

Our previous reports demonstrated that hyperthermia reduces the expression and kinase activity of multiple MAP3K members, such as RAF1 and MLK3, through repression of gene expression or protein denaturation without reduction of the downstream components in the ERK cascades (Enomoto et al., 2019; Enomoto et al., 2022; Enomoto et al., 2024). Additionally, heat shock failed to stimulate the activation of A-Raf proto-oncogene, serine/threonine kinase (ARAF), BRAF, and RAF1 (Ng and Bogoyevitch, 2000). RAF1 stimulates cell proliferation and facilitates cell survival by inhibiting apoptosis (Huang et al., 2017; Wang et al., 2023). Therefore, hyperthermia-induced degradation of

RAF1 and MLK3 may hinder the transmission of proliferative stimuli into activation signals and/or activate downstream targets through phosphorylation, resulting in the inhibition of cell survival and anti-apoptotic signaling, thereby contributing to thermal killing. Previous reports demonstrate that the phosphorylation of ERK1/2 was observed under milder heat shock conditions (42°C), whereas its phosphorylation was suppressed under more severe heat shock (43°C \leq), with a reduction in MAP3K expression (Ng and Bogoyevitch, 2000; Li et al., 2017). Mild hyperthermia enhances NADPH oxidase activity via the ERK pathway followed by HIF-1 α activation with subsequent increased VEGF-secretion (Vaupel et al., 2023). During mild hyperthermia, ERK1/2 may be active and involved in cell survival, the inhibition of apoptosis and tumor angiogenesis.

Hyperthermia stimulates the release of cytokines. Thus, during hyperthermia, TAK1 may be active and involved in immune activation through NF- κ B (Lin et al., 2015; Takaesu et al., 2003). Moreover, treatment with heat increases ROS generation, leading to activation of a ROS-responsive protein kinase ASK1. However, thermal treatment also induces an increase in intracellular calcium and protein degradation. We demonstrated that hyperthermia reduced the expression and kinase activity of TAK1 and ASK1 in the JNK pathway through calpain- or proteasome-dependent protein degradation (Enomoto et al., 2022; Enomoto et al., 2024). Hyperthermia can attenuate NF- κ B activity by decreasing upstream kinase TAK1 activity, leading to the inhibition of cell survival and anti-apoptotic signaling. The degradation of ASK1 may be incapable of transducing apoptotic stimuli into activation signals and/or activating each downstream target through phosphorylation, resulting in the inhibition of JNK signaling. However, the phosphorylation of downstream JNK increased in a temperature-dependent manner, at least up to 43°C (Enomoto et al., 2024). Moreover, heat shock activates JNK independently of upstream kinases, and the exposure of cells to heat shock strongly reduces the dephosphorylation rate of JNK but not p38 (Meriin et al., 1999), indicating its specificity for JNK. A precise balance between the activation and inactivation of the JNK signaling pathway should be strongly regulated for the maintenance of cellular homeostasis. Our recent report demonstrated that dual specificity phosphatase 16 (DUSP16), a JNK phosphatase, was degraded in a proteasome-dependent manner by hyperthermia and that the knockdown of DUSP16 enhanced the heat-induced phosphorylation of ASK, SEK1, and JNK (Enomoto et al., 2024). Another previous report demonstrated that the JNK phosphatase M3/6, namely, DUSP8, is inactivated by heat shock at 45°C (Palacios et al., 2001). DUSPs dephosphorylate both threonine/serine and tyrosine residues of their substrates. A subfamily of DUSPs contains the MAP kinase-binding or kinase-interacting motifs that regulate the magnitude and duration of signal transduction of the MAPK/JNK signaling pathway by dephosphorylating their substrates (Kondoh and Nishida, 2007; Ha et al., 2019). Although DUSP16 can bind to all three MAPKs, it preferentially inactivates JNK1/2, followed by p38 α / β MAPK (JNK1/2 \gg p38 MAPK $>$ ERK) (Masuda et al., 2001); this indicates that hyperthermia may prevent DUSP16 from dephosphorylating JNK but not either p38 or ERK. A recent report demonstrated that DUSP16 inhibits the activation of

JNK, thereby reducing apoptosis and promoting cancer chemoresistance (Low et al., 2021). Some members of the DUSP family also regulate signaling upstream of JNK. DUSP14 directly dephosphorylates TAB1, leading to inhibition of the TAB1-TAK1 complex and sequential inactivation of TAK1 and downstream JNK activity (Yang et al., 2014). Thus, hyperthermia may reduce the ability of DUSP16 to directly dephosphorylate not only JNK but ASK1 and SEK1, leading to enhancement of ASK1-SEK1-JNK signaling and subsequent induction of apoptosis.

Additionally, for heat-induced JNK activation, there are alternatives, such as the involvement of other MAP3Ks, except for the aforementioned kinases. Because the 21 characterized MAP3Ks activate known MAP2Ks (Nguyen et al., 2022), certain heat-resistant MAP3Ks may stimulate MAP2Ks and MAPKs in JNK signaling pathway. In addition, if hyperthermia results in inactivation of the SEK1 phosphatase as protein phosphatases 2A (Avdi et al., 2002), it could lead to JNK activation. During mild hyperthermia, ERK1/2 may be active and involved in cell survival and the inhibition of apoptosis. Hyperthermia, specifically at 43°C or higher, can disrupt the balance between ERK and JNK activation through decrease of MAP3Ks expression in ERK pathway or a reduction in JNK phosphatase function, thereby resulting in the amplification of JNK signaling and enhanced apoptosis (Figure 2). Thus, cellular homeostasis in hyperthermia may be maintained through regulation or deregulation of MAPK signaling to enhance survival, stimulate immunity, or induce cell death at different temperature.

6 Conclusion

MAPK signaling pathways participate in various physiological processes, including cell proliferation, death, and tumorigenesis (Braicu et al., 2019; Wu et al., 2019). Hyperthermia induces the activation of ERK, p38, and JNK signaling pathways. The efficiency of hyperthermia depends on the temperature and duration of heat treatment, which affects the activity of each MAPK. The dynamic balance between the ERK and JNK signaling pathways is crucial in determining whether a cell survives or undergoes apoptosis (Xia et al., 1995). Although JNKs stimulate or inhibit cell death in a context-dependent manner, sustained activation of JNK is necessary for the induction of apoptosis (Dhanasekaran and Reddy, 2017; Yue and López, 2020). The sustained activation of JNK requires multifaceted activation of the JNK signaling pathway under appropriate conditions. For example, hyperthermia reduces JNK phosphatase function, resulting in the sustained phosphorylation of ASK1, SEK1, and JNK and subsequent apoptosis. Further studies should be conducted to explore the mechanisms underlying the JNK signaling pathway during hyperthermia.

Author contributions

AE: Supervision, Writing–review and editing, Writing–original draft, Investigation, Funding acquisition, Formal Analysis, Data

curation. TF: Writing–review and editing, Visualization. AY: Writing–review and editing, Visualization, Validation.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported, in part, by grants from the Ministry of Education, Culture, Sport, Science, and Technology of Japan (20K08100) and by the Japan Health and Research Institute.

Conflict of interest

TF and AY belong to the Social Cooperation Program, Department of Clinical Cannabinoid Research, supported by the

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