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REVIEW

Mnk kinase pathway: Cellular functions and biological outcomes

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Abstract

The mitogen-activated protein kinase (MAPK) interacting protein kinases 1 and 2 (Mnk1 and Mnk2) play important roles in controlling signals involved in mRNA translation. In addition to the MAPKs (p38 or Erk), multiple studies suggest that the Mnk kinases can be regulated by other known kinases such as Pak2 and/or other unidentified kinases by phosphorylation of residues distinct from the sites phosphorylated by the MAPKs. Several studies have established multiple Mnk protein targets, including PSF, heterogenous nuclear ribonucleoprotein A1, Sprouty 2 and have lead to the identification of distinct biological functions and substrate specificity for the Mnk kinases. In this review we discuss the pathways regulating the Mnk kinases, their known substrates as well as the functional consequences of engagement of pathways controlled by Mnk kinases. These kinases play an important role in mRNA translation *via* their regulation of eukaryotic initiation factor 4E (eIF4E) and their functions have important implications in tumor biology as well as the regulation of drug resistance to anti-oncogenic therapies. Other studies have identified a role for the Mnk kinases in cap-independent mRNA translation, suggesting that the Mnk kinases can exert important functional effects independently of the phosphorylation of eIF4E. The role of Mnk kinases in inflammation and inflammation-induced malignancies is also discussed.

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Key words: Mnk kinases; mRNA translation; Mitogen-activated protein kinase signaling; eIF4E phosphorylation; Drug resistance; Cytokine production; Cytokine signaling

Core tip: The Mnk kinases are important downstream targets of the Erk and p38 mitogen-activated protein kinase (MAPK) pathways and their activity can also be modulated by MAPK independent signals. The Mnk kinases play important roles in regulating mRNA translation and, because of this, are key mediators of oncogenic progression, drug resistance, production of pro-inflammatory cytokines and cytokine signaling. This review focuses on the pathways regulating the Mnk kinases, the substrates on the Mnk kinases as well as the biological functions of the Mnk kinases.

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INTRODUCTION

The Erk (extracellular regulated kinase) and p38 (mitogen-activated protein kinase) MAPK pathways are known to play important roles in mediating multiple biological processes including development, apoptosis, autophagy, oncogenesis, inflammation, *etc*[1]. Kinases that can be

phosphorylated by multiple MAPKs such as the MAPK interacting protein kinases (Mnks) can exert multiple biological functions due to their ability to respond to a wide range of external stimuli such as mitogens as well as stress inducers[1]. The Mnk kinase family includes Mnk1 and Mnk2 which were originally discovered in two independent screens as substrates for Erk1[2] and Erk2[3]. It is now well established that the Mnk kinases can be activated by either Erk or p38 MAPKs in response to multiple extracellular stimuli and phosphorylate their major downstream effector, the cap binding eukaryotic initiation factor 4E (eIF4E)[4].

Mnk1 and Mnk2 are serine/threonine kinases with substantial similarity in their coding sequences and motifs present in their structures[3]. Both kinases contain a N-terminal basic amino acid rich region that can mediate their localization; a catalytic domain similar to the serine/threonine kinases such as the Rsks, Ca21/calmodulin (CaM)-dependent kinases, Mapkap kinase-2 and Mapkap kinase-3 containing conserved MAPK phosphorylation sites; and an MAPK binding domain in their carboxyl terminus[3]. Mnk1 is activated in response to treatment with growth factors, ultraviolet (UV) radiation, mitogens and stress inducing agents such as anisomycin or sorbitol as well as by cytokines such as type Ⅰ and type Ⅱ interferons (IFNs), tumor necrosis factor (TNF)-α, interleukin (IL)-1β, *etc.*[3-6]. In contrast Mnk2 exhibits high basal activity that is more resistant to the inhibition of Erk and p38 and these observations can be partially explained by differences in the C-terminal domains of the Mnk kinases[3,7].

A detailed look at the Mnk kinases has shown that both Mnk1 and Mnk2 undergo alternative splicing[8,9]. Mnk1 and Mnk2 transcripts are alternatively spliced giving rise to two distinct isoforms for each[8,9]. The b isoforms lack the MAPK binding C-terminal domain and therefore their activity is MAPK independent[8,10,11]. The b isoforms also lack a nuclear export sequence while still retaining the nuclear localization signal and therefore both Mnk1b and Mnk2b are preferentially localized to the nucleus and in PML bodies which also contain eIF4E[8,10]. While most of the studies on the Mnk kinases have focused on the Mnk1a and Mnk2a isoforms, evidence suggests that aberrant regulation of Mnk splicing can have important biological consequences. The splicing factor SF2/ASF which can function as a proto-oncogene in multiple human cancers can regulate Mnk2 splicing[12]. Overexpression of SF2/ASF was shown to result in the increased expression of the MAPK independent Mnk2b isoform, while knockdown of SF2/ASF attenuated the expression of Mnk2b[12]. This study suggests the need for a better understanding of the factors that regulate Mnk splicing as the preferential expression of the MAPK independent Mnk isoforms can have important biological implications.

POST TRANSCRIPTIONAL REGULATION OF MNK KINASES

Mnk kinase activity is mainly regulated by the upstream p38 and Erk MAPK pathways. The p38 MAPK pathway is activated by a variety of stress inducers such as osmotic shock, UV radiation, as well as cytokine and chemokine stimulation[13]; while engagement of the Erk MAPK pathway is primarily mediated by pro-growth stimuli such as growth factors and phorbol esters[1]. Thus the Mnk kinases can play a dual role in mediating cellular responses to stress as well as responses to mitogens in a context-specific manner. MAPK phosphorylation of Mnk1 results in the phosphorylation of Thr 209 and Thr 214 located in the T loop activation domain, whereas mouse Mnk1 is phosphorylated on Thr 197 and Thr 202[14].

Phosphorylation of Mnk1 has been shown to activate its kinase activity as well as to enhance its binding to the eukaryotic initiation factor 4G (eIF4G) which functions as a scaffolding protein[14,15]. Additionally Mnk1 mediated phosphorylation of eIF4E regulates its release from eIF4G[14]. eIF4G contains binding sites for the cap binding eIF4E and the poly A tail protein (PABP) at the N-terminus[16,17] while the C-terminal domain contains docking sites for eIF3, eIF4A and Mnk1[15,17]. eIF4G along with its binding partners and the small ribosomal subunits are important components of the 48S initiation complex required for translation initiation[18]. Studies suggest that Mnk1 is unable to interact with eIF4E in the absence of eIF4G and a mutant eIF4E lacking the ability to bind eIF4G is not a good Mnk1 substrate[15]. Additionally Mnk1 can interact with the eIF4G related translational repressor p97[15]. p97 which functions as a cap dependent and cap independent translation repressor has a 28% homology to the C-terminal of eIF4G and can interact with translation initiation factors such as eIF3, eIF4A but is unable to interact with the mRNA recruiting eIF4E[19]. Thus p97 may be a potential negative regulator of Mnk1 mediated phosphorylation of eIF4E [15]. Also PKCα which was initially believed to be a Mnk1 kinase is known to phosphorylate eIF4G on Ser 1186 facilitating its binding to Mnk1[20] and may potentially play an important role in regulating Mnk1 activity by indirectly controlling the phosphorylation of eIF4E. Mnk2 has also been shown to interact with eIF4G and to function as an eIF4E kinase[21]. Thus, regulation of the Mnk-eIF4G interaction can play an important role in regulating Mnk activity.

Other studies have suggested that phosphorylation of Mnk1 by the p21 activated kinase 2 (Pak2/γ-Pak) can negatively regulate its kinase activity[22]. Pak2 belongs to a family of serine/threonine kinases and is activated in response to stress inducing stimuli such as UV and ionizing radiation induced DNA damage, serum starvation, by the binding of the GTP bound small G protein cdc24 as well as by caspase 3 mediated cleavage[23]. Caspase 3 activated Pak2 mediated engagement of Mnk1 results in the phosphorylation of Thr 22 and Ser 27, residues that lie in the N-terminal domain of Mnk1 that can interact with eIF4G and thereby attenuates the affinity of Mnk1 towards eIF4G[22]. Additionally Pak2 mediated engagement of Mnk1 also attenuated Mnk1 mediated phosphorylation of eIF4G[22]. As the experiments conducted in this study were for the most part performed *in vitro*,

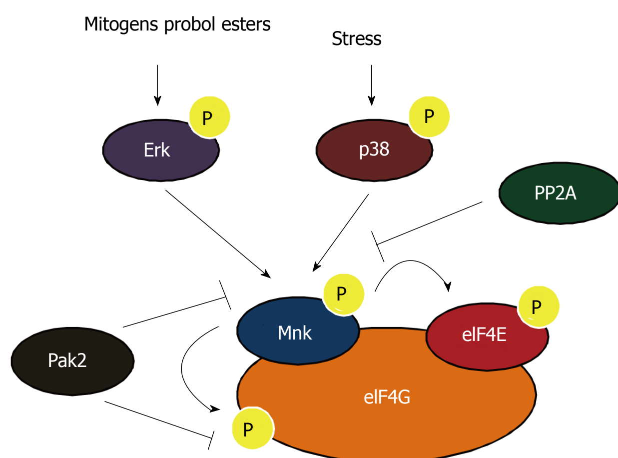

Figure 1 Regulation of Mnk kinases. The Mnk kinases are phosphorylated on Thr 197/202 by the p38 and Erk1/2 mitogen-activated protein kinases (MAPKs). They can associate with eIF4G and this interaction is essential for the efficient phosphorylation of their target eIF4E. The Mnk kinases are also known to phosphorylate eukaryotic initiation factor 4G (eIF4G) but its functional consequences remain to be determined. Pak2 can phosphorylate Mnk1 on Thr22/Ser27 resulting in decreased affinity for eIF4G and potentially interferes with Mnk1 mediated phosphorylation of eIF4E. Additionally Pak2 also phosphorylates eIF4G inhibiting its interaction with eIF4E. Protein phosphatase 2A (PP2A) is a phosphatase for Mnk1 and thereby negatively regulates Mnk kinase activity.

Pak2 mediated phosphorylation of Mnk1 did not affect Mnk1 mediated phosphorylation of eIF4E. Additionally Pak2 can also phosphorylate eIF4G at the eIF4E binding domain and compete with eIF4E to bind eIF4G, thereby exerting suppressive effects on cap dependent translation[24]. These results suggest that Mnk activity may be modulated independently of the MAPK pathway and may account for the observation that all stimuli that result in phosphorylation of Mnk1 do not result in activation of eIF4E on serine 209.

Mnk kinase activity can be negatively regulated by the protein phosphatase 2A (PP2A)[25]. Small interfering RNA mediated knockdown of PP2A or pharmacological inhibition of PP2A was found to result in increased phosphorylation of its direct target Mnk1 and subsequently increased phosphorylation of eIF4E[25]. Phosphorylation of eIF4E in response to PP2A inhibition leads to increased cap dependent translation of growth promoting mRNAs such as c-myc and Mcl-1[25].

Multiple studies have shown that Mnk2 has high basal activity that is mostly unresponsive to external stimuli. A study by Stead *et al*[26] showed that treatment of cells with rapamycin, the classic inhibitor of the mammalian target of rapamycin (mTOR), resulted in enhanced phosphorylation of eIF4E that was mediated by the enhanced activity of Mnk2 and not by Mnk1. The increase in Mnk2 activity was mediated by the decrease in phosphorylation of Mnk2 on Ser 437 by an unidentified mechanism[26]. These results suggest that Mnk2 activity may also be possibly modulated independently of the MAPK pathway. The regulation of Mnk kinases by upstream signaling proteins is summarized in Figure 1.

EFFECTORS OF THE MNK KINASES

The Mnk kinases function as serine/threonine kinases and are known to phosphorylate a number of downstream targets including eIF4E[3,21], hnRNPA1[27] and Sprouty2[28]. Additionally Mnk1 and Mnk2 can also exhibit substrate specificity[29], resulting in substrates that are unique to Mnk1 and Mnk2, respectively. Recent studies have surprising uncovered a kinase independent function for Mnk2 in negatively regulating eIF4G and p70S6K phosphorylations[30]. The proteins that regulate signaling downstream of the Mnk kinases are discussed in detail and are summarized in Figure 2.

eIF4E

A major and well characterized target of the Mnk kinases is the cap binding protein eIF4E. eIF4E is phosphorylated on Ser 209[31] by the Mnk kinases[3] but its role in regulating mRNA translation remains undetermined. Multiple biochemical studies have shown that phosphorylation of eIF4E reduces its affinity for the 5' m7G cap[32,33]. Based on X-ray crystallography data, Scheper *et al*[34] have speculated that the phosphate group on Ser 209 may negatively interact with the phosphate groups on the RNA backbone as well as the mRNA cap. They have put forth a model in which Mnk mediated phosphorylation of eIF4E after the formation of the pre-initiation translation complex leads to the release of eIF4E and thereby enables it to be available for another round of initiation of mRNA translation[34].

Studies based on the targeted deletion of Mnk1 and Mnk2 in mice have suggested that the expression of Mnk1 and/or Mnk2 and the phosphorylation of its target eIF4E is dispensable for survival[35]. Mice with a targeted deletion of Mnk1 and/or Mnk2 do not exhibit any developmental or reproductive defects[35]. Additionally the mouse studies also confirmed previous reports that Mnk1 is more sensitive to external stimuli as mitogen mediated eIF4E phosphorylation was defective in the Mnk1-/- cells, while basal eIF4E phosphorylation was attenuated in Mnk2-/- cells[35]. Mouse embryonic fibroblasts and adult tissues from mice lacking both Mnk1 and Mnk2 did not exhibit any basal or inducible eIF4E phosphorylation indicating that the Mnk kinases are key regulators of eIF4E phosphorylation[35]. Interestingly, cells from Mnk1 and Mnk2 deficient mice did not exhibit any defects in cap dependent translation or general protein synthesis, indicating that Mnk mediated phosphorylation of eIF4E is not critical under basal conditions but may be important during their activation with external stimuli[35].

Similarly knock-in mice expressing a mutant eIF4E (eIF4E S209A) which cannot be phosphorylated do not exhibit any developmental or viability defects[36]. These results suggest that while phosphorylation of eIF4E may not be critical for general mRNA translation, it may be

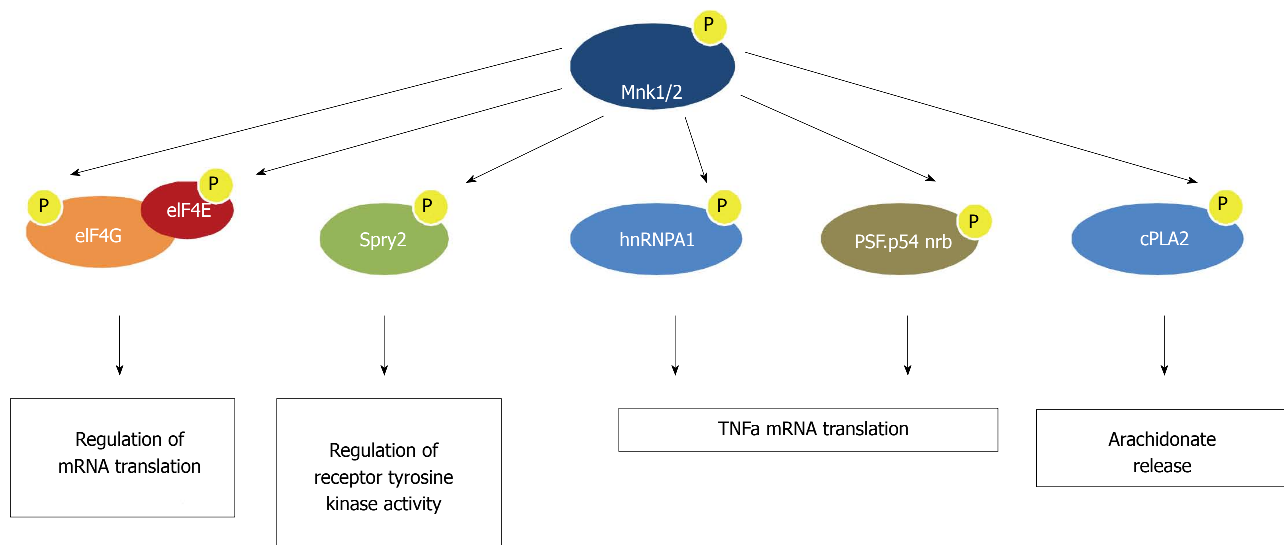

Figure 2 Effectors of the Mnk kinases. The Mnk kinases can regulate multiple biological processes by phosphorylating multiple substrates. Mnk mediated phosphorylation of eIF4E and eIF4G can play an important role in mediating cap dependent translation. The Mnk substrates hnRNPA1 and PSF play an important role in mediating the translation of AU rich elements containing mRNAs such as the TNF-α mRNA. The Mnk kinases also phosphorylate cPLA2 which plays an important role in arachidonate release from platelets. TNF-α: Tumor necrosis factor-α; eIF4G: Eukaryotic initiation factor 4G; hnRNPA1: Heterogenous nuclear ribonucleoprotein A1; cPLA2: Cytosolic phospholipase A2.

important for the translation of specific mRNAs, induced by specific stimuli. Phosphorylation of eIF4E is important for the translation of mRNAs containing 5' untranslated terminal regions (UTRs) with extensive secondary structure[37].

Besides its ability to bind capped mRNA, nuclear eIF4E can interact with a 100 nt eIF4E-sensitive element (4E-SE) region in the 3'UTRs of mRNAs and promote the nuclear export of the bound mRNA[38]. The phosphorylation of eIF4E on Ser 209 is required for its mRNA export activity, as well as transformation[39]. Mnk-mediated phosphorylation of eIF4E can facilitate the nuclear export of mRNAs such as HDM2[40], Cyclin D1[38] and other growth regulatory mRNAs[41].

Sprouty 2

Sprouty2 (Spry2) belongs family of proteins homologous to the Drosophila melanogaster Spry[42] that acts as a negative regulator of multiple receptor tyrosine kinase pathways[43,44] by negatively controlling the Erk MAPK pathway[45]. A study by DaSilva *et al*[28] showed that Mnk1 can phosphorylate Spry2 on Ser 112 and Ser 121 leading to increased stability of Spry2. Inhibition of Mnk activity resulted in increased tyrosine phosphorylation of Spry2 leading to increased binding of c-Cbl and promoting the polyubiquitination of Spry2; consequently resulting in a proteosome mediated decrease in Spry2 expression[28]. Additionally a mutant Spry2 (S112A and S121A) that cannot be phosphorylated by Mnk1 also increased proteosomal degradation of Spry2[28]. Mnk1 mediated stabilization of Spry2 was found to be functionally important for the antagonism of fibroblast growth factor (FGF) signaling by Spry2[28].

Another study showed that Mnk2 can regulate the phosphorylation of Spry2 on Ser 112 and Ser 121[46]. This study established that Mnk2-mediated phosphorylation of Spry2 increased its interaction with the E3 ubiquitin ligase NEDD4 and lead to increased proteosomal targeting of Spry2[46]. Additionally, small interfering RNA mediated silencing of Mnk2 attenuated Spry2 NEDD4 interactions and enhanced the ability of Spry2 to inhibit FGF signaling[46]. The results of the studies by DaSilva *et al*[28] and Edwin *et al*[46] are conflicting, but it is important to note that the studies were conducted in distinct biological cell lines. It is possible that Mnk kinases negatively or positively regulate Spry2 expression in a cell-specific manner, depending on the presence of additional regulatory cellular signals. More work focusing on the relevance of Mnk mediated phosphorylation of Spry2 is required to get a better understanding of the consequences of Spry2 phosphorylation by Mnk kinases.

Studies in our laboratory have previously shown that the Mnk kinases are activated by both type Ⅰ and type Ⅱ interferons (IFNs)[5,6]. IFNs are potent antiviral agents that also generate antiproliferative and antitumor responses[47,48]. Both type Ⅰ and type Ⅱ IFN mediated engagement of the Mnk kinases is important for regulating the inhibitory effects of IFNs on normal hematopoiesis by regulating the translation of specific IFN stimulated genes[5,6]. Importantly, engagement of Mnk kinases also play a critical role in mediating the anti-neoplastic effects of IFNs on primitive myeloproliferative neoplasm (MPN) precursors from patients with polycythemia vera[49]. Other work in our laboratory has shown that type Ⅰ IFNs can upregulate the expression of both Spry1 and Spry2 in a Mnk1 and Mnk2 dependent manner[50]. Data from mouse embryonic fibroblasts (MEFs) derived from mice with a targeted deletion of Spry1, Spry2 and Spry4 suggests

lack of Spry expression promotes IFN mediated antiviral responses[50]. The Spry 1, 2, 3 triple knockout MEFs exhibit enhanced activation of the p38 MAPK pathway in response to IFN treatment and, consequently, enhanced transcriptional activity and expression of the IFN stimulated gene ISG15[50]. Additionally knockdown of either Spry1, Sry2 or Spry4 was found to result in enhanced anti-leukemic effects of type I IFNs[50]. Thus, Mnk mediated phosphorylation of Spry proteins can have important biological consequences, but more work is required to elucidate the role of Mnk mediated phosphorylation of Spry proteins and its biological relevance in response to tyrosine kinase signaling.

hnRNPA1

The Mnk pathway plays an important role in production of TNF-α *via* its effector hnRNPA1. TNF-α is mainly secreted by activated macrophages and T lymphocytes and plays important roles in regulating inflammation[51]. Enhanced secretion of TNF-α is implicated in diseases such as rheumatoid arthritis, and inflammatory bowel disease[52], as well as in superantigen-induced septic shock[53]. Thus, the mechanisms regulating its expression have important clinical-translational and therapeutic relevance. The TNF-α mRNA is tightly regulated by the AU rich elements (AREs) present in the 3'UTR that regulate its nuclear cytoplasmic export[54], mRNA stability[55] as well as its mRNA translation[56]. TNF-α production in activated macrophages, as well as T cells, is regulated by the p38 and Erk MAPK pathways[57,58], consistent with the concept that their common downstream effectors, Mnk kinases may play an important role in TNF-α production.

Buxade *et al*[27] showed that inhibition of Mnk1 activity/expression results in attenuated production of TNF-α in T cells. In that study, overexpression of Mnk1 resulted in increased expression of a reporter construct tagged with the TNF-α 3'UTR suggesting that Mnk1 regulation of TNF-α may be mediated by the AREs[27]. Mnk1 was found to phosphorylated the TNF-α ARE binding protein hnRNPA1 on Ser 192 and Ser 310/311/312 resulting in the disassociation of hnRNPA1 from the TNF-α 3'UTR[27]. Thus, during T cell activation, activation of the MAPK cascade leads to the engagement of Mnk1 and the phosphorylation of its target hnRNPA1 and its disassociation from the TNF-α ARE, consequently promoting the translation of the TNF-α mRNA[27]. ARE elements have also been identified in mRNA encoding cytokines (GM-CSF, IL-3, IFNγ, *etc*.), proto-oncogenes (bcl, c-myc etc.) as well as in nuclear transcription factors (c-fos, c-jun, junB, *etc*.)[59] suggesting that the Mnk kinases can mediate the translation of multiple mRNAs independently of translation initiation complex.

Guil *et al*[60] showed that stress induced engagement of the Mnk kinases results in the phosphorylation of hnRNPA1 leading to its accumulation in stress granules. Depletion of hnRNPA1 or the Mnk kinases attenuates cell recovery following osmotic stress, suggesting that Mnk-mediated recruitment of hnNPA1 to stress granules plays an important role in regulating cell physiology possibly by controlling the expression of stress responsive mRNAs[60]. Many stress inducing stimuli can lead to senescence and this pathway[61,62] may potentially be mediated by the Mnk kinases due to their engagement by the stress activated p38 MAPK pathway. Mnk1 phosphorylation and expression is enhanced in senescent diploid human fibroblasts as compared to young fibroblasts[63]. In senescent cells, Mnk1 can phosphorylate hnRNPA1 leading to the cytoplasmic accumulation of hnRNPA1. Depletion of hnRNPA1 results in induction of senescence[64], suggesting that Mnk kinases may potentially regulate cellular senescence by regulating the cellular distribution of hnRNPA1.

PSF

Buxade *et al*[29] sought to identify novel substrates for the Mnk kinases. Using a proteomic approach, the researchers examined the ability of the Mnk kinases to phosphorylate proteins that could bind to a 5' cap resin[29]. They identified PSF [the PTB (polypyrimidine tract-binding protein)-associated splicing factor] as a potential Mnk substrate[29]. *In vitro* studies showed that the Mnk kinases could phosphorylate PSF on Ser 8 and Ser 283[29]. Remarkably, phosphorylation of PSF on Ser 8 was preferentially mediated by Mnk2 suggesting that Mnk1 and Mnk2 exhibit distinct substrate specificities[29]. PSF along with its partner p54 (nrb) was found to bind mRNAs containing AREs in their 3'UTR, and Mnk mediated phosphorylation of PSF was found to enhance its binding to the TNF-α mRNA containing AREs[29]. Notably, Mnk mediated phosphorylation of PSF did not affect the stability or the nuclear cytoplasmic localization of PSF or the bound TNF-α mRNA, but its effects on TNF-α mRNA translation were undetermined[29]. Thus another Mnk substrate can bind ARE elements in the 3'UTR of mRNAs again underscoring the role of Mnk kinases in mediating mRNA physiology independently of the cap translation initiation complex.

Cytosolic phospholipase A2

Cytosolic phospholipase A2 (cPLA2) is an enzyme activated by increased cytosolic calcium and catalyzes the release of arachidonate acid from glycerophospholipids to provide the precursor of the eicosanoids[65]. Eicosanoids are important secondary messenger molecules that play an important role in inflammation, immunity as well as regulation of the central nervous system[66]. Mnk1 was found to phosphorylate cPLA2 on Ser 727 resulting in the enhancement of its enzymatic activity[65]. Thrombin mediated platelet activation was found to result in Mnk1 mediated engagement of cPLA2 and arachidonate release[65]. Thus the Mnk kinases can play a role in regulating arachidonate acid release and thereby mediate eicosanoid signaling. Although no follow-up studies on the regulatory effects of the Mnk pathway on cPLA2 have been reported, further studies in that direction may provide important insights regarding the role of Mnk kinases

in various cellular and biological contexts.

Mnk2 specific interactions

The Mnk2 kinase was initially identified in a yeast two hybrid screen attempting to identify proteins that can interact with the ligand binding domain of the estrogen receptor β (ERβ)[9]. Only the nuclear Mnk2b isoform and not Mnk2a or Mnk1 was found to specifically interact with ERβ and not ERα[9]. Interestingly esterdiol treatment was found to augment Mnk2b binding to ERβ[9], but whether this interaction leads to the phosphorylation of ERβ or alters ERβ mediated transcription remains to be determined. Another study has reported that ERβ can be phosphorylated on Ser 105 by estradiol-mediated Erk1/2 activation or osmotic stress induced p38 MAPK activation and this phosphorylation was found to inhibit breast cancer migration and invasion[67]. These observations suggest that ERβ may be a potential substrate for the Mnk kinases.

Mnk2 has also been shown to phosphorylate plectin on Ser 4642[68]. Plectin is an ubiquitously expressed protein that can interact with microtubules, intermediate filaments and the actin microfilaments; and thereby plays an important role in regulating cellular responses to mechanical stress[69]. Mnk2 mediated plectin phosphorylation was found to attenuate plectin interactions with the intermediate filaments and reduced plectin phosphorylation was observed at sites of cell substrate contact that require a network of intermediate filaments[68]. These results suggest a potential role for Mnk kinases in mediating cytoskeletal integrity.

A study by Hu *et al*[30] showed that Mnk2 expression is augmented during muscle atrophy. Overexpression of Mnk2, but not Mnk1, was found to attenuate eIF4G phosphorylation on Ser 1108 and reduced basal p70 S6 kinase (p70S6K) phosphorylation at Thr 389 and Ser 371 in a kinase independent manner[30]. The serine-arginine rich protein kinase family members SRPK1, SRPK2 and SRPK3 were identified as the kinases that mediate eIF4G phosphorylation on Ser 1108[30]. Results from *in vivo* studies showed that dexamethasone treatment or starvation of Mnk2 knockout mice resulted in enhanced phosphorylation eIF4G Ser 1108 as compared to the wild type mice[30]. Mnk2 was found to selectively interact with the mammalian target of rapamycin complex 1 (mTORC1) , in a kinase independent manner and this interaction was essential to regulate Mnk2 mediated decreased phosphorylation of p70S6K[30]. As phosphorylation of eIF4G Ser 1108 and p70S6K Thr 389 and Ser 371 is associated with enhanced mRNA translation, these observations suggest Mnk2 may play an important role in negatively regulating protein synthesis during muscle atrophy[30]. These observations are consistent with other findings showing that overexpression of Mnk kinases can negatively regulate cap dependent translation[70] and suggest that Mnk mediated regulation of mRNA translation may be context dependent. Altogether, the available evidence indicates that Mnk1 and Mnk2 exhibit differing substrate specificities and, possibly, distinct biological functions. The functional differences between Mnk1 and Mnk2 need to further explored in future studies using both *in vitro* and *in vivo* approaches.

BIOLOGICAL FUNCTIONS OF THE MNK KINASES

There is extensive and definitive evidence that Mnk kinases regulate the phosphorylation and/or activity of proteins involved in diverse cellular functions. As a result of such effects, the Mnk kinases play important roles in cancer biology, development of drug resistance to cancer therapeutics, cap independent translation, as well in mediating pro-inflammatory cytokine production and cytokine signaling (Figure 3).

Role of Mnk kinases in tumorigenesis

eIF4E is known to be upregulated in a variety of human cancers and is linked to poor prognosis[71]. Additionally, overexpression of eIF4E in NIH-3T3 and rat 2 fibroblasts results in their oncogenic transformation[72]. As eIF4E is modulated by phosphorylation by Mnk kinases, Mnk kinases and phosphorylated eIF4E may have important roles in cancer biology (reviewed in[73]). Studies with mouse models using a rapid adoptive transfer strategy suggest that a constitutively active Mnk1 leads to increased eIF4E phosphorylation and promotes lymphomagenesis by preventing apoptosis and/or by upregulating mRNA translation of the anti-apoptotic Mcl-1[74].

Mouse embryonic fibroblasts derived from mice with a targeted deletion of both Mnk1 and Mnk2 are resistant to Ras mediated transformation[75]. Deletion of both Mnk1 and Mnk2 in a T-cell specific Pten null lymphoma model resulted in delayed tumorigenesis and lymphomas with an absence of eIF4E phosphorylation[75]. Additionally knock-in mice expressing a mutant eIF4E (S209A) that cannot be phosphorylated are resistant to oncogenic transformation by both c-myc and a constitutively active Ras[36]. Additionally the knock-in mice are resistant to Pten loss-induced prostate cancer and exhibit decreased expression of proteins involved in tumorigenesis such as vascular endothelial growth factor (VEGF) and matrix metalloprotease 3 (MMP3)[36]. Moreover, phosphorylated eIF4E positively correlates with progression to human prostate carcinoma[36]. Other studies have shown that inhibition of Mnk activity and the consequent decrease in the phosphorylation of eIF4E strongly attenuates the polysomal recruitment of terminal oligopyrimidine messenger RNAs (TOP mRNAs) and results in decreased expression of mRNAs involved in proliferation in prostate cancer[76].

The Mnk kinases are overexpressed in glioblastoma and inhibition of the Mnk kinases results in attenuated cell growth and increased sensitivity to rapamycin[77]. Additionally, inhibition of Mnk activity was found to attenuate mRNA translation of a subset of genes involved

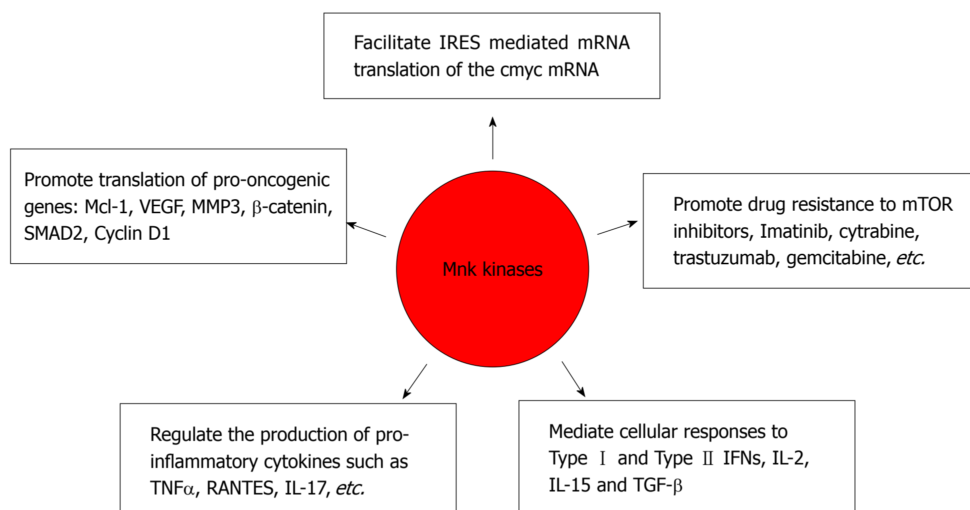

Figure 3 Biological functions of Mnk kinases. The Mnk kinases play an important role in multiple biological processes. Mnk1/2 can regulate tumor biology by mediating the translation of multiple genes that promote tumor growth and resistance to apoptosis. They also mediate resistance to chemotherapy as well as targeted therapy agents such as trastuzumab, imatinib, gemcitabine, *etc*. Mnk kinases are also implicated in regulating cap dependent translation of oncogenes as well as viral mRNA. Additionally the Mnk kinases play an important role in mediating the production of multiple pro-inflammatory cytokines such as TNF-α, RANTES and IL-17 and also mediate cellular responses to multiple cytokines such as Type Ⅰ and Type Ⅱ IFNs, IL-2, IL-15 and TGF-β. TNF-α: Tumor necrosis factor-α; IL: Interleukin; RANTES: Regulated upon activation normal T cell expressed and presumably secreted; TGF: Transforming growth factor; MMP3: Matrix metalloprotease 3; IRES: Internal ribosome entry sites; IFNs: Interferons.

in transforming growth factor β (TGFβ) signaling and regulation of signal transduction and induced cell cycle arrest[77]. A microarray analysis of polysomal mRNA revealed an important role for Mnk kinases in mediating the mRNA translation of SMAD2[77]. Importantly, SMAD2 expression positively correlated with Mnk1 expression in human glioblastoma patients and Mnk1 was found to play an important role in mediating TGFβ induced cell motility[77].

The phosphorylation of Mnk1 and Mnk2 is elevated in Her-2 over-expressing breast cancers and inhibition of Mnk activity can attenuate growth in soft agar[78]. Inhibition of Mnk activity in breast cancer cell lines exerts a cytostatic effect by downregulating the expression of Cyclin D1, one of the targets of phosphorylated eIF4E[79]. In breast cancer cell lines, the integrin α6β4 interaction leads to the engagement of the Mnk kinases in a p38 and Erk dependent manner and enhances VEGF mRNA translation[80].

The Mnk kinases are also known to play a role in hematological malignancies. Acute myeloid leukemia (AML) is often characterized by expression of different fusion proteins that account for leukemic transformation[81]. A microarray study demonstrated that MNK1 is post-translationally stabilized by PML-RAR alpha[82]. Notably, inhibition of Mnk1 activity/expression was found to enhance ATRA (all-trans retinoic acid) induced myeloid differentiation[82]. Another recent study has shown that chronic myeloid leukemia (CML) patients exhibiting blast crisis are characterized by enhanced Mnk-eIF4E phosphorylation consequently leading to augmented β-catenin protein synthesis as well as its nuclear translocation and activation[83]. These results suggest that inhibition of the Mnk kinases may have potential anti-leukemic properties.

Thus the Mnk kinases can play an important role in tumor progression and the development of Mnk inhibitors will have an important clinical applications.

Role of Mnk kinases in drug resistance

Mnk kinases can modulate multiple aspects of tumor biology and data from multiple studies suggest that they may also be involved in drug resistance by multiple mechanisms. Inhibition of mTOR by drugs such as temsirolimus (CCI-779), everolimus (RAD001), and ridaforolimus (AP-23573) has shown promising results in preclinical studies and are under investigation in cancer clinical trials[84]. Numerous studies in our laboratory as well as others have shown that rapamycin treatment of cancer cells results in the phosphorylation of the Mnk kinases as well as its target eIF4E[26,85] in a phosphoinositide 3-kinase (PI-3K) dependent manner[86]. In malignant hematopoietic cells, rapamycin treatment leads to a phosphorylation of Mnk1 and its target eIF4E, while simultaneous inhibition of both mTOR and Mnk kinases enhances the anti-leukemic effects of rapamycin[85]. Additionally Mnk1 inhibition has been shown to augment the anti-tumor effects of rapamycin in multiple human lung cancer cell lines[86]. In prostate cancer cells, inhibition of mTOR or the Mnk kinases results in distinct changes in translation initiation and the simultaneous inhibition both kinases exerts additive negative effects in the recruitment of TOP mRNAs and strong suppressive effects on cell cycle progression[76].

CML is characterized by the t(9; 22) translocation resulting in the constitutively active fusion oncogene bcr-abl, and its inhibition by imatinib mesylate (imatinib) results in a potent patient responses[87]. However, patients with late stage disease often develop resistance to imatinib resulting in decreased drug efficacy[88,89]. A study by Zhang *et al*[90] showed that simultaneous inhibition of the Mnk

kinases and imatinib treatment resulted in a synergistic enhancemet of the anti-leukemic effects of imatinib by augmenting its anti-proliferative and apoptotic effects. Inhibition of the Mnk kinases was found to attenuate polysomal mRNA recruitment by enhancing imatinib mediating inhibition of the pre-initiation complex eIF4F and by independently inhibiting the phosphorylation of the pre-initiation complex associated ribosomal protein S6 (rpS6)[90]. Additionally inhibition of the Mnk kinases has been found to also enhance the anti-leukemic effects of the chemotherapeutic drug cytarabine, currently in clinical use for the treatment of acute myeloid leukemia (AML)[85].

Breast cancers with overexpression of the oncogenic Her-2 are clinically treated with trastuzumab (herceptin), a monoclonal antibody targeting the ectodomain of Her-2[91]. Breast cancer patients that respond to trastuzumab often develop resistance within a year of initiation of treatment[92], underscoring a need to uncover the mechanisms contributing to drug resistance. The oncogenic Y-box-binding protein-1 (YB-1) can be phosphorylated by the p90 ribosomal S6 kinase as well as Akt promoting its nuclear translocation, upregulating the expression of the epidermal growth factor (EGFR), MET, PIK3CA and CD44 ultimately conferring trastuzumab resistance[93]. Using an unbiased chromatin immune-precipitation sequencing approach to identify the transcriptional targets of YB-1, Astanehe *et al*[94] identified Mnk1 as a YB-1 transcriptional target. Mnk1 and Mnk2 were found to be overexpressed in trastuzumab resistant cell lines and depletion of Mnk1 was found to augment trastuzumab sensitivity[94]. Consistently, overexpression of Mnk1 was sufficient to confer trastuzumab resistance[94] suggesting a causative role for Mnk1 in the process.

Pancreatic ductal adenocarcinoma (PDAC) is clinically treated with the chemotherapeutic drug gemcitabine which results in marginal benefits when used as a single agent[95]. A study by Adesso *et al*[96], showed that eIF4E phosphorylation positively correlates with PDAC tumor grade and predicts a ppor prognosis. *In vitro* studies showed that gemcitabine treatment can induce eIF4E phosphorylation in a Mnk2 dependent and Mnk1 independent manner[96]. Gemcitabine was found to induce the expression of the oncogenic splicing factor serine/arginine rich splicing factor (SRSF1) which preferentially promoted the expression of the MAPK independent Mnk2b isoform with high basal activity[96]. Interestingly, inhibition of Mnk activity synergistically enhanced the anti-oncogenic effects of gemcitabine by promoting apoptosis suggesting an important role for Mnk2 and SRSF1 in mediating gemcitabine resistance[96].

Thus the Mnk kinases can regulate resistance to chemotherapy as well as targeted therapy in multiple cancer types. The clinical development of Mnk inhibitors may therefore play an important role in enhancing the efficacy of cancer therapeutics.

Role of Mnk kinases in cap independent translation

The role of Mnk kinases in cap dependent translation had been the subject of extensive work, but more recent evidence suggests that the Mnk kinases may also play an important role in mediating cap independent translation. Cap independent translation is mediated by the internal ribosome entry sites (IRES) in the 5'UTR of the target mRNAs[97,98]. The IRES elements possess complex secondary and tertiary structures that facilitate the interaction with the 40S ribosome in the absence of eIF4E and other translation initiation factors[99]. IRES elements can thereby facilitate mRNA translation when cap dependent translation is impaired in virus infected cells[100] or in malignant cells treated with drugs inhibiting cap dependent translation[101] .

Cap dependent translation is often dis-regulated in malignant cells and drugs inhibiting cap dependent translation are in common clinical use. Studies in multiple neoplastic cell types have suggested that cancer sensitivity to rapalogs is decreased by induction of the Akt pathway[102,103] subsequently resulting in IRES mediated translation of oncogenes such as VEGF[104], cyclin D1 and c-myc[105]. Interestingly, the IRES mediated translation of oncogenes is also regulated by the p38 and Erk MAPK pathways[105] suggesting a role for the Mnk kinases in controlling cap independent translation. A recent study by Shi *et al*[106] demonstrated that mTOR inhibition by rapamycin in multiple myeloma cells results in the activation of Mnk1. Inhibition of Mnk activity or expression was found to attenuate rapamycin induced upregulation of c-myc IRES activity[106]. Combination treatment of malignant cells with rapamycin and a Mnk inhibitor was found to abolish c-myc expression and enhanced the anti-oncogenic activity of rapamycin[106].

Additional evidence from viral studies also supports a role for the Mnk kinases in the regulation of IRES mediated translation. A study by Goetz *et al*[107] showed that replication and cytotoxicity of the prototype oncolytic poliovirus PVSRIPO in glioblastoma multiforme (GBM) results in the engagement of Mnk1 subsequently resulting in the enhanced cap independent translation of the viral RNA[107]. Taken together, these results suggest that Mnk kinases play important roles in regulating cap independent translation and more studies along this line are required to gain mechanistic insight into such effects.

Role of Mnk kinases in inflammation

MAPK pathways such as Erk and p38 have been shown to play important roles in modulating immune responses by mediating the production of cytokines that control the initiation of innate immunity; the activation of adaptive immunity; and by regulating cellular responses to cytokines involved in immune responses[108]. As Mnk kinases are effectors of MAPK pathways, these observations suggest that they may play important roles in mediating cytokine production at the translational level. Indeed pharmacological blockade of Mnk kinases was found to attenuate the production of pro-inflammatory cytokines such TNF-α, IL-6, and monocyte chemo-attractant protein-1 and enhanced the production of the anti-inflam-

matory cytokine IL-10 in macrophages stimulated with multiple Toll like receptor (TLR) agonists[109]. Also, data from multiple studies have shown that Mnk kinases play important roles in mediating the production of multiple pro-inflammatory cytokines such as TNF-α, RANTES and IL-17 and in mediating the cellular responses to Type Ⅰ and Type Ⅱ IFNs, IL-2, IL-15 and TGF-β (reviewed in[110]).

Most of the studies focusing on the role of the Mnk kinases in inflammation have utilized small interfering RNA mediated Mnk knockdown or pharmacological inhibitors of the Mnk kinases. Recently a study by Gorentla *et al*[111], examined the role of Mnk kinases in T cell development in mice with a targeted deletion of Mnk1 and Mnk2. This study showed that in mice lacking Mnk1 and Mnk2, T-cell receptor mediated Ser 209 phosphorylation of eIF4E in T cells was completely abolished[111]. Lack of of Mnk1 and Mnk2 expression in T cells had no influence on the development of conventional αβ T cells, regulatory T cells, or NKT (natural killer T cells)[111]. The Mnk1/2 double knockout mice also did not exhibit any deficiencies in CD8 T cell response to bacterial or viral infection[111]. Interestingly, while lack of the Mnk kinases does not inhibit Th1 and Th17 differentiation *in vitro*, immunization of mice with myelin oligodendrocyte glycoprotein peptide in complete Freund's adjuvant, an experimental model of autoimmune encephalomyelitis, resulted in attenuated production of IFNγ and IL-17 by CD4 T cells and attenuated differentiation of Th1 and Th17 cells[111]. Collectively, these results suggest that while the Mnk kinases are dispensable for normal T cell development and function, they may play important roles in regulating the cytokines required for T cell differentiation or antigen presenting cell (APC) activation pathways, and thereby modulate Th cell differentiation in an T cell extrinsic manner[111].

Another recent study focused on the role of the Mnk kinases in the generation of neutrophil responses. Neutrophils are involved in acute inflammatory response and secrete proinflammatory cytokines such as TNF-α, IL-1β, IL-8, IFNγ, IL-4, IL-10, *etc*.[112]. Mnk1 is phosphorylated in human neutrophils upon treatment with LPS or TNF-α[113]. Inhibition of the Mnk kinases in LPS or TNF-α stimulated human neutrophils was found to attenuate the secretion of CXCL8, CCL-3 and CCL4 while the mRNA levels of the cytokines were unaffected, Mnk inhibition also attenuated the anti-apoptotic effects of LPS and TNF-α[113]. Overexpression of a kinase active Mnk1 and not a kinase dead Mnk1 mutant was found to enhance LPS- and TNF-α- induced cytokine secretion[113]. Similarly the Mnk kinases play important roles in pro-inflamatory cytokine production in macrophages[109]. These studies further support the observation that the Mnk kinases are attractive targets for diseases associated with inflammation.

While pro-inflammatory cytokines play an important role in mediating an effective immune response to pathogens, their persistent enhanced expression is associated with multiple disorders such as auto-immune diseases[114], allergies[115], neurological disorders[116], sepsis[117], cardiovascular diseases[118], obesity[119] and cancer[120]. As the Mnk kinases represent a central node in regulating pro-inflammatory cytokine production, development of Mnk inhibitors will have important broad spectrum translational implications.

CONCLUSION

The Mnk kinases are regulated by the p38 and Erk MAPK pathways and their activity can also be modulated by other MAPK independent mechanisms. Multiple proteins such as those involved in mRNA translation (eIF4E, eIF4G), in TNF-α mRNA expression (hnRNPA1, PSF), in platelet activity (cPLA2) and in regulation of receptor tyrosine kinase activity (Spry2) are regulated by the Mnk kinases. As a result, the Mnk kinases can play important roles in controlling cap-dependent and -independent translation, participate in the pathophysiology of several malignant and inflammatory diseases and diminish responses to cancer therapeutics (Figure 3).

The above observations suggest that development of Mnk inhibitors can have broad spectrum clinical applications. Most of the studies discussed in this review used the Mnk inhibitor CGP57380 a low weight molecular compound identified from the Novartis Pharma compound collection that can inhibit both Mnk1 and Mnk2 activity[121]. The IC_{50} of CGP57380 against Mnk1 is seen at a concentration of 2.2 μmol/L[70], the concentration at which it can also inhibit the activity of other kinases such as casein kinase, MAP2K1 and BR serine/threonine-protein kinase 2[122]. As a result this compound cannot be used for *in vivo* studies and research mainly utilizing CGP57380 should be interpreted with caution. The antifungal agent cercosporamide is also reported to inhibit Mnk activity, although it exhibits higher specificity for Mnk2 as compared to Mnk1[123]. Importantly cercosporamide has been shown to exhibit anti-tumor effects in both *in vitro* and *in vivo* studies[123, 124]. More research efforts are needed to develop Mnk inhibitors that can be tested in clinical settings.

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