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Review

Role of MAPK/MNK1 signaling in virus replication

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\textbf{A B S T R A C T}

Viruses are obligate intracellular parasites; they heavily depend on the host cell machinery to effectively replicate and produce new progeny virus particles. Following viral infection, diverse cell signaling pathways are initiated by the cells, with the major goal of establishing an antiviral state. However, viruses have been shown to exploit cellular signaling pathways for their own effective replication. Genome-wide siRNA screens have also identified numerous host factors that either support (proviral) or inhibit (antiviral) virus replication. Some of the host factors might be dispensable for the host but may be critical for virus replication; therefore such cellular factors may serve as targets for development of antiviral therapeutics. Mitogen activated protein kinase (MAPK) is a major cell signaling pathway that is known to be activated by diverse group of viruses. MAPK interacting kinase 1 (MNK1) has been shown to regulate both cap-dependent and internal ribosomal entry sites (IRES)-mediated mRNA translation. In this review we have discuss the role of MAPK in virus replication, particularly the role of MNK1 in replication and translation of viral genome.

1. Introduction

Cell signaling is a part of a complex system of communication through which living cells interact with the neighbouring cells and extracellular environment (Denef, 2008). Cells are equipped with glycoproteins or glycolipid receptors on the plasma membrane through which they respond to changes in their immediate environment. When a complementary ligand (signaling molecule) binds to the receptor, it initiates a chain of events within the cell called signal transduction, ultimately resulting into a response. This ability of the cells to respond to their microenvironment solely determines growth, development, tissue injury/repair, cell homeostasis and immunity. A cell can communicate signals to neighbouring cells in multiple ways, which include: direct transfer of ions/small molecules through pores in the membrane, endocrine signaling that utilizes hormones, paracrine signaling by secreting chemicals into the common intercellular space, autocrine signaling to alter its own extracellular environment, juxtacrine signaling by making physical contact with adjacent cells and synaptic signaling (nervous system) (Brucher and Jamali, 2014).

Cell signaling starts with an external stimuli (signals); most cell signals are chemical in nature but mechanical stimuli are also possible (Cargnello and Roux, 2011). Cells employ numerous intracellular signaling pathways for transmitting information within the cell. However, a cross talk among these cell signaling pathways is quite possible (Vert and Chory, 2011). The signaling pathways may be activated in response to external stimuli or via the messengers (ligand/information/metabolic) that are generated within the cell following insults. The information in signaling pathways is conveyed either through protein-protein interactions or via diffusible elements usually referred to as second messengers (Cargnello and Roux, 2011).

2. MAPK signaling

Mitogen activated protein kinase (MAPK) is an important cell signaling pathway that converts extracellular stimuli into a wide range of cellular responses (Cargnello and Roux, 2011). MAPK signaling is activated by a variety of chemical and physical stimuli such as cytokine, hormone, growth factors, pathogens (including viruses), osmotic stress, heat, oxidative stress and microtubule disorganization (Boulton et al., 1990; Raman et al., 2007; Rose et al., 2010; Widmann et al., 1999). MAPK pathway regulates gene expression, mitosis, cell survival, apoptosis, metabolism and cell differentiation (Roux and Blenis, 2004; Shaul and Seger, 2007). The information in MAPK pathway is transmitted via protein-protein interactions. By phosphorylating serine and threonine residues in diverse groups of proteins, MAPKs convert a variety of extracellular signals into a multitude of cellular responses (Ceballos-Olvera et al., 2010; Shi et al., 2013).

MAPK signaling toolkit is composed of a cell surface receptor that
receives extracellular signals in the form of chemical or mechanical ligand, a transducer that converts extracellular stimuli into intracellular signals. MAPK module has three evolutionary conserved, sequentially acting proteins namely, MAPK kinase kinase (MAPKKK), MAPK kinase (MAPKK) and MAPK (Fig. 1). Their downstream targets include MAPK scaffolding protein and MAPK target protein (effectors protein) (Cargnello and Roux, 2011). To be enzymatically active, these proteins must undergo phosphorylation (Robbins et al., 1993).

Extracellular signal-regulated kinase (ERK, also known as p42/44 MAPK), Janus kinase (JNK, also known as stress activated protein kinase-1, SAPK1) and p38 MAP kinase (also known as SAPK2/RK) are three major MAPK pathways in mammals (Gaur et al., 2011; Ludwig et al., 2006). ERK1 and ERK2 are key transducers of proliferation signals and are often activated by mitogens. JNKs and p38 poorly respond to mitogens but are strongly activated under cellular stress (Cargnello and Roux, 2011). Following activation, these cytosolic proteins (MAPK downstream molecules) either remain in cytoplasm or may translocate into the nucleus to activate numerous proteins and transcription factors (Cuadrado and Nebreda, 2010; Li et al., 2016) (Fig. 1). These regulatory molecules not only transmit information to the target effectors but also cross talk with other parallel signaling pathways. These mechanisms allow amplification of the signals and generate a threshold for activation of diverse pathways (Cargnello and Roux, 2011; Maroni et al., 2004).

In order to manipulate cellular functions in its favor, viruses interact with MAPK family members- ERK, p38 and JNK. MAPK pathway is
| Signaling pathway | Cellular mediator | Impact on virus replication | References |
|-------------------|-------------------|-----------------------------|------------|
| RTK family        | Ab1               | Positively regulates transport and release of poxviruses (Reeves et al., 2005) |
|                   | EGFR              | Facilitates vaccinia virus spread (Langhammer et al., 2011) |
|                   | VEGF              | Facilitates ORFV replication and formation of pox-like lesions (Wise et al., 1999) |
|                   | Src kinase        | Positively regulates assembly, maturation and egress of WNV (Hirsch et al., 2005) |
|                   | NGFR              | Positively regulates RNA synthesis, vRNP export and release (budding) of IAV (Kumar et al., 2011a) |
|                   | PDGFR             | Facilitates KSHV tumor progression (Cao et al., 2015; Sturzl et al., 1992) |
| GPCRs             | GPCRs             | Promotes membrane fusion and cell to cell spread in hHSV6 mediated via US1 protein (Zhen et al., 2005) |
|                   | N-Ras             | Positively regulates reovirus replication and spread (Shmulevitz et al., 2010) |
|                   | Akt               | Promotes clathrin-independent endocytosis and internalization of IAV (Fujioka et al., 2011) |
| Ras/Akt           | Ras               | Positively regulates HSV1 replication and transcription (mediated via HSV1 transcriptional transactivating protein Hbx) (Hube et al., 2005) |
|                   | Raif              | Positively regulates enterovirus replication (Huber et al., 1999) |
|                   | Ras-GTP           | Positively regulates parvovirus transport across nuclear membrane as well as capsid assembly (Riolobos et al., 2010) |
|                   | Ras-GTP cleavage  | Positively regulates synthesis and release of HSV-1 (Flory et al., 1998) |
|                   | RKIP              | Modulation of immune response to NDV (Yin et al., 2015) |
|                   | MEK               | Facilitates IAV nuclear export (Ludwig et al., 2004; Pleschka et al., 2001) |
| Ras/Raf/MEK/ERK   | Ras               | Positively regulates reovirus replication and spread (Shmulevitz et al., 2010) |
|                   | Ras-GTP           | Positively regulates HBV replication and transcription (mediated via HBV transcriptional transactivating protein Hbx) (Benn and Schneider, 1994; Tang et al., 2005) |
|                   | Cleavage of RasGAP| Positively regulates enterovirus replication (Huber et al., 1999) |
|                   | Raif              | Positively regulates parvovirus transport across nuclear membrane as well as capsid assembly (Riolobos et al., 2010) |
|                   | RKIP              | Modulation of immune response to NDV (Yin et al., 2015) |
|                   | MEK               | Facilitates IAV nuclear export (Ludwig et al., 2004; Pleschka et al., 2001) |
|                   | p38               | Positively regulates reovirus replication and spread (Shmulevitz et al., 2010) |
|                   | JNK               | Positively regulates reovirus replication and spread (Shmulevitz et al., 2010) |
| Ras/p38           | p38               | Positively regulates reovirus replication and spread (Shmulevitz et al., 2010) |
| Ras/JNK           | JNK               | Positively regulates reovirus replication and spread (Shmulevitz et al., 2010) |
| MNK1/eIF4E (cap-dependent translation) | Phosphorylation of eIF4E | Positively regulates HSV-1 genome and protein synthesis (Walsh and Mohr, 2004) |
|                   | mTORC1-mediated hypophosphorylation of 4E-BP1 | Facilitates IAV protein synthesis (Ikeguchi et al., 1996) |
| MNK1/SRPK (cap-independent translation) | Inhibition of mTOR/akt signaling | Facilitates HSV-1 replication and translation (Chu and Yang, 2007) |
|                   | PCB2-mediated recruitment of PIC | Positively regulates poivirion genome synthesis (Chase et al., 2014) |
|                   | SRPK              | Facilitates poivirion genome synthesis (Chase et al., 2014) |
|                   | elf4G-mentions     | Facilitates poivirion genome synthesis (Chase et al., 2014) |
| PKR               | elf2a             | Facilitates poivirion genome synthesis (Chase et al., 2014) |
|                   | PP2 A             | Negatively regulates DNA synthesis in simian virus 40 (Cegelska et al., 1994) |
activated by a wide variety of viruses (Table 1). Depending on the nature of virus, MAPK signaling may either support or down regulate virus replication (Rodriguez et al., 2014). Moreover, MAPK signaling activated by virus independent sources can also be misused by the viruses to facilitate their own replication. For instance, phorbol-12-myristate-13-acetate (PMA) and new born calf serum activate MAPK; arenaviruses use this enhanced activity to promote its own replication (Rodriguez et al., 2014). Such widespread exploitation of MAPK pathway by viruses suggests that it may be used as a target to develop broad-spectrum antiviral drugs.

Depending on the nature of the virus involved, MAPK signaling may regulate single or multiple steps of virus replication (Andrade et al., 2004). For example, Ebola virus entry (Han and Harty, 2007), assembly and budding/release of HIV-1 (Hemonnot et al., 2004), replication/transcription of HCV (Pei et al., 2012), IAV protein synthesis (Gaur et al., 2011) and reactivation of KSHV latency (Jham and Montaner, 2010; Xie et al., 2008). Besides, it also regulates immune response (Gaur et al., 2011) and apoptosis (Bian et al., 2011) in virus infected cells.

Both live as well as inactivated virus can activate MAPK signaling pathway at a similar level (Rodriguez et al., 2014). Moreover, some viral secretory proteins can also lead to sustained activation of MAPK. For example, vaccinia virus growth factor (VGF) (secretary polypeptide from vaccinia virus homologous to epidermal growth factor (EGF) and transforming growth factor (TGF)) can effectively stimulate ERK1/2 (Andrade et al., 2004).

2.1. Cell surface receptor for MAPK signaling

Cell-surface receptors are specialized integral membrane proteins that constitute a major route by which signals are conveyed from extracellular to the intracellular environment of the cells. Cell surface receptors sense the extracellular signals by binding to their cognate ligands and are of three types, ligand-gated ion channel receptor (Leite and Cascio, 2001), enzyme-linked receptor and G protein-coupled receptor (GPCR) (Jordan and Devi, 1999). In MAPK signaling, receptor tyrosine kinase (RTKs, enzyme linked receptors) and GPCRs are the major classes of cell surface receptors (Widmann et al., 1999), though integrins may also activate MAPK signaling (Widmann et al., 1999). Besides MAPK signaling, RTKs and GPCRs may also be implicated in regulation of phosphoinositide 3-kinase (PI3K)-Akt signaling pathway (Rajagopalan, 2010).

2.1.1. RTKs

RTKs are the high-affinity cell surface receptors for many growth factors, cytokines and hormones (Lemmon and Schlessinger, 2010). Besides being key regulator of normal cellular processes, RTKs also play a critical role in the development and progression of several types of cancer (Bennasroune et al., 2004). Mutations in RTKs lead to the dysregulation of a series of signaling cascades that may eventually develop disease syndromes. (Lemmon and Schlessinger, 2010). RTKs are members of the large family of proteins that contain a trans-membrane domain, an extracellular N terminal region, and an intracellular C terminal region. The cytoplasmic C terminal region of RTKs is highly conserved, encompassing kinase activity and catalyses receptor autophosphorylation including tyrosine phosphorylation of RTK substrates (Segaliny et al., 2015). Tyrosine kinase that does not possess any trans-membrane domains also exists and is called as non-receptor tyrosine kinase. Currently, over 20 different RTK classes have been identified viz; epidermal growth factor receptor (EGFR), insulin receptor family, platelet derived growth factor receptor (PDGFR), vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR), cholecystokinin receptors (CCKR), nerve growth factor receptor (NGFR), hepatocyte growth factor receptor (HGF), ephrin receptor, AXL receptors, tyrosine kinase with immunoglobulin-like and EGF-like domains 1 (TIE1), related to receptor tyrosine kinase receptor (RYRK), discoidin domain receptor, 1 (DDR1), rearranged during transfection (RET), ROS receptor family, leukocyte receptor tyrosine kinase (LTK), receptor tyrosine kinase-like orphan receptor (ROR), muscle-specific kinase receptors (MuSK), lemur tyrosine kinase (LMR), and an undetermined class of RTKs (Segaliny et al., 2015).

Ligand binding induces receptor dimerization and autophosphorylation (Fig. 1). Each RTK has several auto-phosphorylation sites, which recruit different Src homology 2 domains (SH2) and phosphotyrosine binding domain (PTB) containing proteins that have intrinsic enzymatic activity. Binding of SH2 and PTB proteins with auto-phosphorylated intra-cytoplasmic domain of RTK leads to initiation of signal transduction pathways (Lemmon and Schlessinger, 2010). Besides SH2 and PTB, occasionally, adaptor proteins such as src homology 3 domain containing (SH3) and growth factor receptor-bound protein 2 (Grb2), which have no intrinsic enzymatic activity, can also initiate MAPK signaling by recruiting son of sevenless (SOS) protein (Gobert Gosse et al., 2005) (Fig. 1). Taken together, ligand binding to RTK induces RTK-Grb2-SOS-Ras/MAPK signaling (Lemmon and Schlessinger, 2010).

Besides MAPK, RTKs may also activate PI3K/Akt signaling (Cargnello and Roux, 2011; Cattaneo et al., 2014; Schlessinger, 2000) (Fig. 1). Src family of RTKs have been shown to support assembly and maturation of dengue virus (DENV) and West Nile virus (WNV) (Chu and Yang, 2007; Hirsch et al., 2005) and, entry of HIV-1 (Tokunaga et al., 1998) and HSV-1 (Qie et al., 1999). RTKs have also been shown to regulate multiple steps of influenza A virus (IAV) replication, which include RNA synthesis, Crm1-dependent nuclear export and, release of viral particles from infected cells through a pathway that is modulated by the lipid biosynthesis enzyme farnesyl diprophosphate synthase (FPPS) (Kumar et al., 2011a).

2.1.2. GPCRs

GPCRs lack intrinsic enzymatic (kinases) activity and are coupled to heterotrimeric G proteins, which consist of Ga, Gβ and Gγ subunits. Ligand binding induces conformational changes in GPCRs, during which the heterotrimeric G-proteins dissociate in GTP-bound Ga and Gβγ subunits. These dissociated subunits of GPCRs regulate enzymatic activity of several key enzymes including second messengers such as adenylatecyclase, phospholipase C (PLC) which in turn regulate cellular functions by triggering different signaling pathways (Cattaneo et al., 2014; Neves et al., 2002). GPCRs have been shown to promote membrane fusion and cell-to-cell spread of human herpesvirus 6 (Zhen et al., 2012) as well as entry and RNA synthesis in flaviviruses (Le Sommer et al., 2012). Kaposi’s sarcoma-associated herpesvirus (KSHV) oncogenes are associated with dysregulation of angiogenesis, which is mediated via GPCRs (Jham and Montaner, 2010).

2.2. Ras (transducer)

Upon activation, RTKs and GPCRs induce activation of its downstream signaling component-Rat sarcoma (Ras) which functions as GDP/GTP-regulated molecular switch (Biou and Cherfils, 2004). Ras is a 21-kDa protein belongs to the superfamilly of small guanosine triphosphatases (GTPases) and is structurally related to Gα subunit of heterotrimeric G protein. In the inactive state, it binds to the nucleotide guanosine diphosphate (GDP) while in the activated state, binds to guanosine triphosphate (GTP). Ras interacts with and transmits signals to the downstream effector molecules (MAPKKKs/MAPKPs) associated with ERK/JNK/p38 pathway (Rajalingam et al., 2007). The process of exchanging the bound nucleotide is facilitated by guanine nucleotide exchange factors (GEFs) (Li et al., 2016) and GTPase activating proteins (GAPs) (Wennerberg et al., 2005).

Ras has an intrinsic GTPase activity thereby allowing spontaneous conversion of Ras-GTP to Ras-GDP to become inactive (Campbell et al., 1998; Wennerberg et al., 2005) (Fig. 1). Ras-GTP activates rapidly accelerated fibrosarcoma (Raf) which serves as first part of ERK/MAPK cascade. Ras GTPase-activating proteins (Ras-GAP) are the family of
regulatory proteins that bind to activated G proteins and stimulate their GTPase activity, eventually resulting in termination of the signaling event. By stimulating intrinsic Ras GTPase and consequent hydrolysis of GTP to GDP, Ras-GAP negatively regulates Ras-GTP (Bollag and McCormick, 1991; Trubey et al., 1988). Viral infections induce Ras-GAP cleavage which eventually triggers activation of Ras pathway. For example, Coxsackie virus B 3 (CVB3) infection leads to cleavage of Ras-GAP to produce Ras-GTP (activate state) which is required for efficient virus replication (Huber et al., 1999; Luo et al., 2002). Inhibition of MAPK/ERK kinase (MEK), which regulates cleavage of Ras-GAP, results in reduced CVB3 replication (Huber et al., 1999; Luo et al., 2002) (Table 1).

Ras activation depends on GEFs such as SOS and cell division cycle 25 (cdc25) phosphatase. Autophosphorylation of different intracytosolic domains of RTKs (Margolis and Skolnik, 1994) or conformational changes in GPCRs (Della Rocca et al., 1997) activate Ras by recruiting GEFs. Mutations in Ras may lead to persistent activation of Ras (Chappell et al., 2011; Li et al., 2016). Besides GEFs, some adaptor proteins also support MAPK activation. For example, growth factor receptor-bound protein 2 (Grb2), an adaptor protein, recruits SOS and triggers activation of MAPK and PI3K/Akt pathways (Fig. 1). MAPK activation results in transcription of genes involved in cell growth and differentiation (Li et al., 2016; Luo et al., 2002) whereas PI3K/Akt pathway regulates cytoskeleton integrity and apoptosis. Ras has four subtypes viz; Ha-Ras, N-Ras, KiRas 4 A and KiRas 4B of which KiRas strongly activates MAPK pathway (Li et al., 2016; Yan et al., 1998) whereas HaRas more strongly activates PI3K/Akt pathway (Li et al., 2016).

2.3. Raf/MEK/ERK pathway

ERK pathway plays multiple pivotal roles in regulating cell fate (Cagnol and Chambard, 2010; Roux and Blenis, 2004; Shaal and Seger, 2007) and cell cycle progression, thereby serving as a reasonable target for the modulation of viral multiplication. To initiate ERK signaling, Raf interacts with MEK1/2 which in turn activates ERK.

2.3.1. Raf (MAPKKK)

Raf (MAPKKK) serves as first part of ERK/MEK module and holds a pivotal position in the MAPK signaling pathway (Hamden et al., 2005). Three kinases in Raf family viz; Raf-1, B-Raf, and A-Raf, are related with retroviral oncogenes (Roskoski, 2010). Among these, A-Raf serves as a main upstream activator of the ERK pathway (Fig. 1). Activation of Raf kinase involves interaction with Ras-GTPases (Bondeva et al., 2002; Roskoski, 2012). Besides Raf, MEK, Raf has a large number of other substrates such as JAK, PKA, ribosomal acidic P proteins (Rap), Src family kinase, Rac (also known as Ras-related C3 botulinum toxin substrate 1), PI3K, and phosphoinositide-dependent protein kinase-1 (PDK1) (Maroni et al., 2004; Zebisch and Troppmair, 2006).

Raf phosphorylates its downstream targets via MEK/ERK pathway (Czech et al., 2014; Li et al., 2016). Among the Raf family members, only B-Raf (mutated) is able to persistenty activate Raf/MEK/ERK pathway (Garnett and Marais, 2004). Mutated B-Raf can also activate MEK/ERK pathway as well as activating other Raf family members (Li et al., 2016; Rushworth et al., 2006). Furthermore, Ras, but not Raf has an intrinsic GTPase activity, thereby mutations at critical catalytic sites do not result in persistent Raf activation. Three Raf family members may induce MEK activation with varying biological effects in the order of B-Raf > Raf-1 > A-Raf (Alessi et al., 1994; Li et al., 2016). The Raf signaling was shown to regulate calcium/calmodulin-mediated budding of Ebola virus-like particle (VLP) (Han and Harty, 2007). Drugs targeting the Raf-MAPK signaling pathways represent a promising new class of antiviral agents to treat severe acute respiratory syndrome coronavirus (SARS-CoV) and poxvirus infections (Fauci and Chalberg, 2005; Mizutani et al., 2004).

2.3.2. MEK (MAPKK)

MAPK (MEK1/2) are tyrosine and serine / threonine dual specificity protein kinases that are activated by Raf-mediated phosphorylation and are second component of ERK/MAPK module. MEK is the most characterized substrate for Raf (Hamden et al., 2005). The interaction between MAPKPK and its downstream target MAPK is highly specific. Among the three types of MAPKs, p42/p44 (ERK) is phosphorylated solely by MEK 1 and 2, p38 MAPK is selectively activated by MKK3 and MKK6, while JNK is activated by MKK7 and MKK4. However, MKK4 may also activate p38 MAPK upon over expression (Maroni et al., 2004). Activated MEK has been shown to positively regulate borna disease virus (BDV) spread to neighbouring cells (Planz et al., 2001), RNA synthesis of the coronavirus (Cai et al., 2007) and nuclear export of influenza viruses (Ludwig et al., 2004; Pleschka et al., 2001).

2.3.3. ERK

ERK is a key molecule in ERK/MAPK module that is solely activated by dual specificity MEK 1 and 2 (Plotnikov et al., 2011). In order to initiate ERK signaling, Raf interacts with MEK1/2 which in turn activates ERK. ERK1 and ERK2 are two isozymes with 83% amino acid homology and are expressed in diverse tissue types, which can be activated by a large number of extracellular and intracellular stimuli (Shi et al., 2013). Activated ERK can phosphorylate downstream kinases in the cytoplasm, at cell membrane and in the nucleus, thus diversifying the signaling cascade. ERK1/2 has more than 160 downstream target molecules (Li et al., 2016; McBurey et al., 2007) that may phosphorylate different transcription factors, such as Ets-1, c-Jun, cmyc, CREB, NFkB, Elk1, c-Fos, c-Jun and STAT1 (Nakano et al., 1998; Shi et al., 2013; Steelman et al., 2004). NF-kB and STAT1 are rapidly activated in response to viral infections and cytokines, thus modulating the expression of genes involved in proliferation, apoptosis and immune response (Kumar et al., 2008; Levy et al., 2011). Some of the downstream targets such as ribosomal S6 kinase (RSK) family members are solely activated by ERK (Chambard et al., 2007; Roux and Blenis, 2004). RSK is shown to regulate KSHV lytic replication by promoting viral protein translation (Kuang et al., 2011).

Overexpression of the dominant negative mutants of Raf/ERK2 and MEK was shown to block influenza virus (Pleschka et al., 2001) and HCV replication respectively (Gretton et al., 2010). Likewise, overexpression of an active form of the Raf catalytic domain enhances parvovirus (Riolo et al., 2010) and HIV-1 (Flory et al., 1998) replication. These evidences suggest that enhanced signaling activity may be misused by the viruses for their effective replication. For example, IAV interacts with ERK1/2 that allows effective trafficking of viral ribonucleoprotein (vRNP) (Pleschka et al., 2001), viral genome synthesis (Gaur et al., 2011) and induction of immune response, mediated via RANTES (regulated on activation, normal T cell expressed and secreted) (Kujime et al., 2000). Adenovirus type 7 activates Raf/MEK/ERK pathway that results in induction of IL-8 which plays an important role in viral pathogenesis (Alcorn et al., 2001). ERK2 is involved in regulating HIV-1 virion assembly and release by phosphorylating p6Gag (Hemonnot et al., 2004; Snyder et al., 2010). In HCV infection, MAPK/ERK pathway regulates viral RNA translation by directing the viral genome towards IRES (Pei et al., 2012). By regulating expression of lytic gene (switching viral latency from latent to lytic phase), MAPK pathway also facilitates Kaposi's sarcoma-associated herpesvirus (KSHV) replication (Xie et al., 2008).

Most common viral infections induce biphasic activation of ERK1/2 in the target cells. First peak of ERK1/2 activation occurs immediately following infection, suggesting that signaling is initiated by binding of the virus to its cognate receptors/co-receptor complex. For instance, engagement of HIV-1 p56ck and/or p59fyn with RTKs leads to ERK activation (Shenoy-Scaria et al., 1992). Only replication-competent (but not UV-irradiated/inactivated) viruses are capable of triggering late ERK activation thereby suggesting that high level of late-phase ERK activation is dependent on accumulation of viral gene/gene products;
the late phase ERK activation is associated with expression of HCV core protein (Shenoy-Scaria et al., 1992) and the HIV-1 Tat protein (Rusnati et al., 2001).

2.4. JNK pathway

In mammals, JNKs are encoded by three distinct genes (JNK1, JNK2 and JNK3). JNK1 and JNK2 are ubiquitously expressed, while JNK3 is limited to brain, heart and testis (Yan et al., 2010). During JNK activation, initial signaling pathway starts with the activation of several MAPKKs including Tak1, MEK1/4, MLK2/3, and ASK1, which phosphorylate MEK4 or MEK7 and thus lead to activation of JNK (Krishna and Narang, 2008) (Fig. 1). JNK induces activation of transcription factors such as NF-κB p65, Elk-1, c-Fos, c-Jun and STAT1 which play a pivotal role in regulating the immune response to viral infections. In addition, activated JNK induces secretion of proinflammatory cytokines (Das and Muniyappa, 2010) such as TNFα, IFNs, IL1, IL2 and IL6 (Ting et al., 2010). JNK is also associated with regulation of apoptosis via modulation of c-Jun/AP1 and transforming growth factor-β (TGf-β) (Xing et al., 2010). Although JNK is important for apoptosis, it also contributes to cell survival. These opposite effects rely on duration and magnitude of the pathway activation as well as concurrent activation of other signaling pathways. Prolonged activation of JNK mediates apoptosis whereas transient activation allows cell survival (Shi et al., 2013). Transient JNK activation is therefore essential for effective virus replication such as HSV-1 (McLean and Bachenheimer, 1999), DENV (Ceballos-Olvera et al., 2010), IAV (Ludwig et al., 2001) and varicella-zoster virus (VZV) (Rahaus et al., 2004).

2.5. p38 MAPK pathway

p38 MAPK pathway modulates macrophase and neutrophil functions including chemotaxis, respiratory burst activity, granular exocytosis, adherence and apoptosis, as well as mediating T cell differentiation and apoptosis, by regulating IFN-γ production (O’Sullivan et al., 2009). MKK3 and MKK6 serve as the major MAPKKs responsible for p38 activation (Derijard et al., 1995). MKK3/6 itself are activated by a number of MAPKKKs, including MEKK1-3, MLK2/3, ASK1, Tpl2, TAK1, and TAOL/2 (Cuadrado and Nebreda, 2010) (Figs. 1 and 2). After activation, p38 phosphorolysates a large number of substrates in both cytoplasm (pPLA2, MNK1/2, MK2/3, Htr, Bax, and Tau) and the nucleus (ATF1/2/6, MEF2, Elk-1, GADD153, Ets1, p53, and MK2/1) (Cuadrado and Nebreda, 2010) (Fig. 1). These transcription factors regulate expression of RANTES, IL-8 and TNF-α, which are believed to regulate proinflammatory responses following viral infections (Medders and Kaul, 2011).

In conclusion, MAPK pathway positively regulates virus replication in diverse group of viruses (Table 1) except herpesvirus, NDV and poliovirus where it has negative impact on virus replication cycle. In herpesviruses and polioviruses, MAPK/ERK function is performed by MAPK/p38/JNK pathway (Table 1).

3. MNK1

MAPK interacting kinase 1 (MNK1) is one of the MAPKs activated kinase encoded by Mnk1 gene (O’Loghlen et al., 2004). It is expressed in all adult tissues except the brain (Waskiewicz et al., 1997) and is mainly activated by ERK1/2, although p38 can also activate it (Hardett et al., 2005; Roth et al., 2017). The downstream enzymatic activity of MNK1 depends on the upstream regulators (ERK1/2 and p38) which phosphorylate it at specific residues; these phosphorylation sites have been mapped using phospho peptide analysis of MNK1 by mass spectrometry (Cargnello and Roux, 2011). MNK1 has several potential downstream substrates, which include (i) eukaryotic initiation factor 4E (eIF4E) and eukaryotic initiation factor 4 G (eIF4 G) that helps in 5′ m7G-dependent mRNA translation and regulate cell growth and proliferation (Richter and Sonenberg, 2005), (ii) heterogeneous nuclear ribonucleoprotein A 1 (hnRNPA1) that facilitates processing, metabolism and transport of pre-mRNA. Besides, it also helps in production of TNFα and plays an important role in regulating inflammation (Locksley et al., 2001), (iii) p54 together with PSF [polypyrimidine tract binding (PTB)-associated splicing factor] form transcription splicing factor that is implicated in diverse biological functions such as alternative processing and translation of RNA, as well as regulation of tissue-specific gene expression (Buxade et al., 2008; Valcarcel and Gebauer, 1997). (iv) Cytosolic phospholipase A2 (cPLA2) leads to production of eicosanoids (a second messenger) and plays an important role in immunity and inflammation (Heffner et al., 2000). (v) Sprouty 2 (Spry2) membrane associated protein negatively regulates ERK/MAPK signaling pathway (Cabrera and Christofori, 2008).

4. Role of MNK in virus replication

Viruses completely depend on the host translational machinery for synthesis of the viral proteins (Walsh and Mohr, 2004), therefore they have developed strategies to modulate host cell translation for optimizing their replication and spread. Viral mRNAs may have a range of structures at its 5′ end. It may be capped with m7G or linked with viral genome-linked proteins (VPg). Uncapped viral mRNAs may carry cis-acting regulatory elements (CREs) such as internal ribosomal entry site (IRES) and protein binding sites. These 5′ end structures have been shown to regulate viral mRNA translation (Brown et al., 2014a). MNK1 is involved in regulating both IRES- and cap-dependent viral mRNA translation.

4.1. Role of MNK1 in initiation of cap-dependent viral mRNA translation

Most DNA viruses such as HSV-1, African swine fever virus (ASFV) (Castello et al., 2009), vaccinia virus (Walsh et al., 2008) as well as some RNA viruses such as chikungunya virus (CHKV) (Walsh et al., 2013), SARS-CoV (Cencic et al., 2011), orthomyxoviruses (Aragon et al., 2000; Yanguze et al., 2012), rhabdoviruses (VSV, rabies virus) (Komarova et al., 2007), reoviruses (Chulu et al., 2010), hantaviruses (Mir and Panganiban, 2008), and alphaviruses (Voss et al., 2014) contain a 5′ cap in their mRNA. Some of the viruses such as influenza virus steal the 5′ cap from the cellular mRNAs (GU et al., 2015; Plotch et al., 1981) whereas several other viruses synthesize it by using host-encoded capping apparatus, for instance, vaccinia virus and reoviruses (Harwig et al., 2017). Viruses such as flaviviruses (Saeedi and Geiss, 2013) and nidoviruses synthesize the 5′ cap by their own capping apparatus (Harwig et al., 2017). Caliciviruses and picornaviruses contain VPg at its 5′end (Chaudhry et al., 2006; Goodfellow et al., 2005). These 5′ end structures in viral genome mimic 5′ m7G cap of the host mRNA, therefore viral RNA is translated like cellular mRNA. These viruses do not completely shutoff host protein synthesis. For initiation of 5′ m7G cap-dependent viral mRNA translation, eIF4 F plays a central role in recruiting protein synthesis machinery to fully process capped mRNAs (Fig. 2). eIF4 F consists of a large adaptor protein eIF4 F that binds with eIF4 E, a cap-binding protein eIF4 A, an RNA helicase (Svitkin et al., 2005), poly(A)-binding protein (PABA) that links 5′ and 3′ ends of properly spliced mRNA (Imataka et al., 1998) and eIF3 that assembles mRNA to the 40S ribosomal subunit.

Activated MNK1 may directly bind to eIF4 E in the initiation complex and phosphorylate eIF4 E which subsequently binds to 5′ cap of mRNA. In resting stage, eIF4 E binding protein 1 (4E-BP1) remains associated with eIF4 E. This dimer gets dissociated by phosphorylation of 4E-BP1 by metabolic sensor-mammalian target of rapamycin (mTORC1), which may be activated by either MNK1 or by ATP (representing high metabolic energy in the cell) (Waskiewicz et al., 1999). MNK1/eIF4 E-mediated viral mRNA translation is known to take place in poxviruses, herpesvirus, alphaviruses, orthomyxoviruses, reoviruses and...
and coronavirus (Table 1).

4.2. MNK1 in initiation of cap-independent viral mRNA translation

Cap-independent translation is usually mediated by IRES which regulates interaction with eIFs and/or ribosomal proteins, and are able to initiate translation in the middle of a mRNA (Jackson, 2013). The mechanism of association of MNK1 with viral IRES-mediated translation is not completely understood. IRES-containing viruses can misuse activated MNK1 only when the classical function of MNK1 is being usurped, i.e., phosphorylation of eIF4E and its binding with eIF4G to form eIF4F complex, to initiation translation (Cuesta et al., 2000) (Fig. 2). Activated MNK1 is misused by the viruses by three distinct mechanisms, which include (i) Dephosphorylation of eIF4E as seen in poliovirus and EMCV (Kleijn et al., 1996). (ii) Cleavage of eIF4G as seen in poliovirus and pestivirus (Kempf and Barton, 2008; Willcocks et al., 2011) and (iii) Inhibiting 4E-BP1 phosphorylation concomitant with recruitment of 40 s PIC, for example adenovirus (Gingras and Sonenberg, 1997) and HIV-1 (Borman et al., 2001). (iii) class III IRES utilize prokaryotic-like mode of translation initiation. By interacting with eIF3 and ribosomes, it facilitates positioning of ribosomes at mRNA (Babaylova et al., 2009; Berry et al., 2010; Locker et al., 2007), for example pestivirus, HCV, HIV-1 (Locker et al., 2011) and simian picornavirus (SPV9) (de Breyne et al., 2008). (iv) class IV IRES directly recruit 40S subunits without utilizing any eIFs, for example members of the family Dicistroviridae (Jan and Sarnow, 2002; Kamoshita et al., 2009; Wilson et al., 2000). Trans-acting host factors such as SRPKs, hNRNPA1 and PSF (MNK1 downstream substrates) interact with the CREs (positive-stranded RNA viruses and ds RNA viruses) to regulate viral RNA replication, subgenomic mRNA synthesis, translation and encapsidation. (Sullivan and Ahlquist, 1997; Pathak et al., 2012; Wang and Zhang, 1999).

MNK1 regulates IRES-containing mRNA translation by modulating SRPK1/2. However, SRPK1/2 is not a direct substrate for MNK1, its being regulated by MNK1-induced mTORC1-mediated inhibition of mTORC2-Akt signaling (Brown et al., 2014b) (Fig. 2). Ser/Arg (SR)-rich proteins (SRPs) that are prime substrates of SRPK1/2 (Brown et al., 2014b) constitute a large family of nuclear phosphoproteins that found

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Fig. 2. Role of MNK1 in viral mRNA translation.

MAPK pathway is activated by binding of the ligands to their cognate receptors (RTKs/GPCRs). With the help of adaptor proteins (SOS/Grb2), activated receptors convert Ras-GDP to Ras-GTP. Further information in the pathway is conveyed by phosphorylation (activation) of a series of enzymes, namely Raf, MEK1/2, and ERK1/2 which leads to activation of MNK1. Alternatively, MNK1 may be activated by p38. Besides regulating cell proliferation, cell survival and immune response, activated MNK1 also regulates viral mRNA translation. Activated MNK1 leads to dissociation of 4EBP1-eIF4E complex, which results in release (mediated via mTORC1) and subsequently phosphorylation of eIF4E. Activated eIF4E is required for assembly of eIF4F to initiate cap-dependent viral mRNA translation. Alternatively, MNK1 may modulate SRPK function by directly inhibiting mTORC2-Akt signaling which is prerequisite for cell survival during viral infection. Activated SRPK phosphorylates SRPs that bind with IRES in the viral genome to initiate cap-independent viral mRNA translation. Activated MNK1 also facilitates pre-mRNA and post-translational processing, mediated via hNRNPA1 and PSF respectively.
in both nucleus and cytoplasm (Sanford et al., 2004) and are associated with host-RNA-processing and alternative splicing. Upon direct interaction with viral mRNA, SRPs facilitates splicing of viral pre-mRNA in SINV, HIV-1, CMV (Fukuhara et al., 2006) and HCV (Karakama et al., 2010).

To recruit PIC in class I and class II IRES containing viruses, the SRPs are also believed to interact with the poly (rC) binding protein 2 (PCBP2) (Bedard et al., 2007). PCBP2 may alter IRES conformation to enhance eIF4G binding, thereby facilitating ribosome recruitment (Blyn et al., 1996; Sweeney et al., 2014). PCBP2/SRP20 interaction is essential for picornavirus mRNA translation (Bedard et al., 2007). However, in IRES class III and class IV, SRPs do not seem to play any role because PIC assembly does not require eIF4G.

MNK1 substrate hnRNP A1 has been shown to colocalize with viral nucleoprotein in the cytoplasm, particularly in the perinuclear region of virus-infected cells (Shi et al., 2000; Wang and Zhang, 1999) and is believed to regulate not only IRES-dependent translation initiation in enteroviruses (Tolbert et al., 2017), but also non-IRES-dependent translation initiation in SINV (Lin et al., 2009) and HCV (Kim et al., 2007; Li et al., 1997).

PSF, another MNK1 substrate has been shown to directly interact with viral mRNA in order to support posttranscriptional processing as well as translation of viral mRNA (Fig. 2). For example, PSF directly interacts with the cloverleaf CVB3 RNA as well as the IRES elements to regulate viral mRNA translation (Dave et al., 2017). In Hepatitis delta virus (HDV), PSF directly binds to the stem loop domain of the viral RNA to regulate viral mRNA translation (Greco-Stewart et al., 2006). MNK1/SPRP mediated viral mRNA translation occurs in flaviviruses, picornaviruses, retroviruses, polyomaviruses and adenoviruses (Table 1).

4.3. Role of MNK1 in viral genome synthesis

CRRs in positive-sense RNA viruses participate in RNA/RNA and RNA/protein interactions, thereby modulating viral RNA replication/transcription/translation as well as encapsidation (Sullivan and Ahlquist, 1997; Liu et al., 2009; Pathak et al., 2012; Wang and Zhang, 1999). MNK1 substrate hnRNP A1 colocalize with viral RNA in the cytoplasm and regulate genome synthesis of coronavirus mouse hepatitis virus (Shi et al., 2000, 2003). Besides MNK1, mTORC1 (which may be activated by both MNK1 and ATP) has also been shown to support synthesis of the viral genome (Waskiewicz et al., 1999). For example, in a study with HCV, activated mTORC1 was shown to support viral RNA synthesis (Stohr et al., 2016) without any direct involvement of MNK1.

4.4. Role of MNK1 in cell survival during viral infection

mTOR is a metabolic sensor of cells with highly conserved serine/threonine residues (Hall, 2008) and is found in two structurally and functionally distinct multiprotein complexes, mTORC1 and mTORC2. mTORC1 is rapamycin sensitive and contains mTOR, regulatory associated protein of mTOR (RAPTOR) and mammalian lethal with SEC13 protein 8 (mLST8). (Hall, 2008). The high ATP/AMP ratio promotes and activates mTORC1, which leads to the dissociation of eIF4E from 4E-BP, ultimately resulting in enhanced protein synthesis (Brett et al., 2014), to support virus replication (Kuss-Duerkop et al., 2017; McNulty et al., 2013; Stohr et al., 2016). Conversely, antiviral role of mTORC1 has been demonstrated in CHIKV where virus has evolved a mechanism to bypass mTORC1 inhibition via MNK1/eIF4E mediated translation (Joubert et al., 2015) (Fig. 2). Antiviral function of mTORC1 in VSV is believed to be due to mTORC1-dependent type I IFN production, and initiation of autophagy (Alain et al., 2010).

mTORC2 is resistant to rapamycin and contains mTOR, rapamycin-insensitive companion of mammalian target of rapamycin (RICTOR), mammalian stress-activated protein kinase-interaction protein 1 (mSIN1), proline-rich protein 5 (PRR5) and mLST8 (Hall, 2008). Energy depletion (low ATP levels) leads to adenosine monophosphate-activated protein kinase (AMPK)-mediated accumulation of AMP, which inhibits mTORC1 and activates mTORC2 (Brett et al., 2014). Upregulation of various apoptotic factors and inflammatory mediators during viral infection leads to cellular stress (reduced ATP level), which results in inactivation of mTORC1 and AMPK-mediated activation of mTORC2. Activated mTORC2 then promotes Akt phosphorylation (Vadakonda et al., 2013) and MNK1 dephosphorylation. The Akt-mTORC2 signaling plays a critical role in survivability of cells under stressful conditions such as: (i) activation of PKGs that maintains microtubule integrity (cytoskeletal dynamics) (ii) controlling ion transport and cellular growth via serine/threonine-protein kinase (SGK1) phosphorylation (iii) inhibiting PKR-mediated inflammatory response and upregulation of interferons (iv) interfering caspase protein and p53 mediated apoptosis and (iv) inhibition of MNK1 that shutoff both cap-dependent and cap-independent translation. This global inhibition of cellular protein synthesis aids in immune evasion (Ersahin et al., 2015; Porta et al., 2014). For example, influenza virus (Kuss-Duerkop et al., 2017), vaccinia virus and cowpox virus (Soares et al., 2009) activate mTORC2-Akt signaling which play a critical role in survivability at late stage of viral infection. However, in a study, DENV polyprotein was found to suppress only host cell translation at the level of translation initiation whereas viral protein synthesis remained unaffected. DENV infection triggered activation of p38/MNK1signaling that eventually resulted in phosphorylation of eIF4E, which was sufficient to translate viral genome (Roth et al., 2017).

4.5. MNK1 signaling in immune response to viral infections

Viruses have evolved strategies to avoid a complete arrest in synthesis of cellular and viral proteins. Many of them directly modulate PKR activity while others inhibit phosphorylation of eIF2α. PKR, a member of eIF2α family of kinases contributes in cellular homeostasis by inhibiting translation of nonessential proteins. It acts as a pattern recognition receptor to sense dsRNA, a replicative intermediate formed in host cells during RNA virus replication. It has three sensor units viz; (i) general control nonrepressed 2 (GCN2) that is activated in response to amino-acid deprivation (ii) PKR-like endoplasmic reticulum kinase (PERK) that is activated in response to overloaded or misfolded proteins in the endoplasmic reticulum and (iii) heme-regulated eIF2α kinase (HRI) that is activated in response to reduced heme levels as well as heat shock (Dang Do et al., 2009). Activated PKR phosphorylates α subunit of eIF2-α as well as activating stress pathways- JNK, p38, NFκB (Fernandes, 2016) and protein phosphatase 2A (PP2A) (Ahn et al., 2007).

PKR is known to antagonize MNK1 (Castello et al., 2009) and Akt signaling (Pataer et al., 2009). Phosphorylated eIF2α antagonize MNK1 functions by arresting both cellular and viral mRNA translation (Srivastava et al., 1998). For example, PKR mediated phosphorylation of eIF2α is shown to inhibit translation of VSV (Connor and Lyles, 2005), rotavirus (Rojas et al., 2010) and alphavirus (Ventoso et al., 2006), besides inducing shutoff of the host cell translational machinery. PKR-mediated activation of NFκB (Dabo and Meurs, 2012), JNK and p38 leads to upregulation of various transcription factors including interferons and cytokines, thereby inducing an antiviral state (Taghavi and Samuel, 2012). PKR-mediated activation of tumor suppressor PP2A A leads to negative regulation of ERK1/2 (Yu et al., 2004) and AKT signaling (Ugi et al., 2004). Inhibition of ERK1/2 impedes MNK1 activation (Waskiewicz et al., 1997) whereas AKT inhibition may negatively affect cell survival (lack of maintenance of microtubule integrity and interference with p53 mediated apoptosis) (Ersahin et al., 2015; Porta et al., 2014), thereby preventing further viral spread and augmenting abortive viral replication. Besides PKR, SPRY2 (MNK1 substrate) also triggers interferon production. In addition, SPRY2 negatively regulates ERK-MNK1 signaling (Cabrita and Christofori, 2008), by upregulating TNFα (Locksley et al., 2001) and eicosanoids (Henfer et al., 2000).
MNK1 substrates- hnRNPA1 and cPLA2 also play an important role in immunity and inflammation.

5. Genome-wide siRNA screens to identify cellular factors required for virus replication

Gene silencing through RNAi includes sequence-specific targeting of mRNAs by delivering 20–25 nucleotide long dsRNA homologous to gene concerned. RNAi has enabled systematic exploration of host genes involved in virus replication and virulence, thereby allowing identification of novel drug targets (Radoshitzky et al., 2016). Since the last decade, a large number of genome-scale RNAi screens have been conducted, which identified cellular factors required for WNV (Krishnan et al., 2016). More comprehensive information about the tested cellular factors required for WNV is summarized in Table 2. More detailed functional analyses of these host genes (identified in genome-wide screens) will provide insights for development of novel antiviral therapeutics.

6. Kinase inhibitors as antiviral agents

In 2002, kinome-the protein kinase complement of the human genome, identified 518 protein kinase genes. Protein kinases play a pivotal role in cellular transduction signaling. Their malfunction, hyperactivity or overexpression is usually associated with disease. Kinase is one of the most intensively studied classes of drug targets (Zhang et al., 2009). Understanding the structural basis of kinase is essential for developing selective inhibitors to target most possible member of the kinome (Cao et al., 2010). Over 80 kinase inhibitors have been evaluated to some stage of clinical trial and over 30 distinct kinase inhibitors have been developed to the level of a Phase I clinical trial (Zhang et al., 2009). The vast majority of these inhibitors were investigated for the treatment of cancer (Player, 2009). However, dysregulation of kinase function has been implicated in several other disorders, including metabolic, immunological, neurological and infectious disease. Most of the known kinase inhibitors target at the kinase activation loop in the ATP binding site (Zhang et al., 2009).

Besides genome-wide siRNA screens, screening kinase inhibitor libraries has also enabled identification of kinases required for efficient virus replication (Kumar et al., 2011a). These inhibitor libraries identified both virus-specific and broad-spectrum antiviral agents (Kumar et al., 2011b). While some of the inhibitors were shown to impair single step of virus life cycle (Kumar et al., 2008), others block multiple steps of virus replication cycle (Kumar et al., 2011a). Kinase inhibitors that target MAPK pathway and may have potential to act as antiviral agents are summarized in Table 2. More comprehensive information about the kinase inhibitors could be accessed elsewhere in several excellent reviews (Bogoyevitch et al., 2004; Burkhard and Shapiro, 2010; Gangwal et al., 2013; Genovese, 2009; Janne et al., 2013; Kim and Sim, 2012; Levitzki and Gazit, 1995; Matsuda and Fukumoto, 2011; Sweeney and Firestein, 2006; Uehling and Harris, 2011; West and East, 2011).
drug resistance at drug sites. After the advent of high throughput genome sequencing and genome-wide siRNA screens, thousands of cellular factors that support virus replication have been identified. Since it’s not quite easy for the virus to replace the missing cellular functions by mutations, host-directed antiviral therapies usually do not induce generation of drug-resistant virus variants. In this review, we have described numerous cellular factors/cell signaling pathways which are exploited by the viruses for their effective replication. These cellular factors may serve as potential drug targets to develop novel antiviral therapeutics. However, their further validation, in vivo efficacy and clinical trials are essential before actually translating them from research into the clinical settings.

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