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REVIEW

Functions of MAP3Ks in antiviral immunity

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Abstract

Immune signal transduction is crucial to the body's defense against viral infection. Recognition of pathogen-associated molecular patterns by pattern recognition receptors (PRRs) activates the transcription of interferon regulators and nuclear factor-κB (NF-κB); this promotes the release of interferons and inflammatory factors. Efficient regulation of type I interferon and NF-κB signaling by members of the mitogen-activated protein (MAP) kinase kinase kinase (MAP3K) family plays an important role in antiviral immunity. Elucidating the specific roles of MAP3K activation during viral infection is essential to develop effective antiviral therapies. In this review, we outline the specific regulatory mechanisms of MAP3Ks in antiviral immunity and discuss the feasibility of targeting MAP3Ks for the treatment of virus-induced diseases.

Keywords Antiviral immunity · Antiviral therapy · IFN-I · MAP3Ks · NF-κB

Introduction

Mitogen-activated protein kinases (MAPKs) are serine/threonine protein kinases involved in cell physiology, cytopathology, and various illnesses, including cancer [1]. The three-layer MAPK cascade includes MAP kinase kinase kinases (MAPKKKs or MAP3Ks), MAP kinase kinases (MAPKKs or MAP2Ks), and MAP kinases (MAPKs) [2–5]. MAP3Ks function as links in signal transmission, providing specificity for stimulus-dependent activation of the MAP2K-MAPK pathway, through distinct protein-protein interactions and phosphorylation of signal effectors [6]. Among the 24 identified MAP3Ks, MAP3K1-21, A-Raf, B-Raf, and C-Raf (Raf-1) belong to the most diverse subfamilies in the MAPK signaling cascade [7, 8]. Different MAP3Ks can phosphorylate the same MAP2K and the same MAP3K can phosphorylate different MAP2Ks (Table 1). MAP3Ks serve as tissue nodes or "hubs" in integrating cellular responses to offer specificity in MAPK activation and functional responses [54].

In the innate immune system, pathogen-associated molecular patterns from viruses are mainly recognized by three PRRs, toll-like receptors (TLRs), retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), and DNA receptors. These will then trigger an immune response pathway that activates type I interferon (IFN-I) and NF-κB signaling for antiviral immunity [55, 56]. IFN-I signaling is strictly regulated. Failure to trigger IFN-I expression can result in severe inflammation, whereas prolonged IFN-I production can contribute to the development of autoimmune diseases [57, 58]. NF-κB can trigger the expression of inflammatory mediators, including cytokines, chemokines, and cell adhesion molecules, thereby exerting antiviral effects [59].

MAP3Ks play several roles during viral infection and have reciprocal effects on virus survival. After viral infection, MAP3Ks regulate the production of interferons, inflammatory mediators, and other antiviral substances through antiviral pathways, which are essential to the host's defense against viral invasion. Elucidating the functions of MAP3Ks during viral infection may help improve our understanding of viral illnesses and facilitate the development of efficient antiviral medications and techniques. Here, we provide an overview of the processes and functions of MAP3Ks in terms of IFN-I and NF-κB signaling. Additionally, we investigated the potential therapeutic benefits of targeting MAP3Ks in conditions caused by viruses such as human

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Table 1 Mechanism of MAP3Ks regulating activity through transcriptional level, allosteric regulation, and post-translational modification

Gene name	Alternative name	Substrate	Examples of MAP3Ks activity regulation	Ref.
MAP3K1	/	MKK1, MKK/4/7	Increasing MAP3K1 mRNA transcription by miR145	[9]
			Oligomerization activates MAP3K1	[10]
MAP3K2	/	MKK5, MKK4/7	Inhibiting of MAP3K2 mRNA transcription after heat stimulation	[11]
			K27-linked polyubiquitination represses MAP3K2 expression	[12]
MAP3K3	/	MKK1, MKK3/6, MKK5	Inhibiting of mRNA transcription by miR-188	[13]
			Phosphorylation activates MAP3K3	[14]
MAP3K4	/	MKK3/6, MKK4/7	Inhibiting MAP3K4 mRNA transcription in intrahepatic cholangiocarcinoma	[15]
			Phosphorylation activates MAP3K4	[16]
MAP3K5	ASK1	MKK3/6, MKK4/7	Increasing ASK1 mRNA transcription by stress exposure	[17]
			14-3-3 binds to the domain of ASK1	[18]
			Deubiquitination leads to inactivation of ASK1	[19]
MAP3K6	ASK2	MKK3/6, MKK4/7	Increasing MAP3K6 mRNA transcription through transient ose-only exposure	[20]
			Phosphorylation activates ASK2	[21]
MAP3K7	TAK1	MKK3/6, MKK4/7	Inhibiting of mRNA transcription after heat stimulation	[11]
			TAB1 activates TAK1 through allosteric regulation	[22]
			Polyubiquitination degrades TAK1	[23]
MAP3K8	TPL2	MKK1, MKK4	Increasing TPL2 mRNA transcription by VEGF-A	[24]
			Inhibitors cause TPL2 conformational changes	[25]
			Phosphorylation activates TPL2	[26]
MAP3K9	MLK1	MKK2, MKK3/6, MKK4/7	Increasing MLK1 mRNA transcription by sodium butyrate	[27]
			MLK3 SH3–interacting peptide (MIP) binds to the SH3 domain	[28]
			Phosphorylation activates MLK1	[29]
MAP3K10	MLK2	MKK2, MKK3/6, MKK4/7	Increasing MLK2 mRNA transcription at day 35 in rats	[30]
			Phosphorylation activates MLK2	[31]
MAP3K11	MLK3	MKK2, MKK3/6, MKK4/7	Inhibiting MAP3K11 mRNA transcription by overexpression MIR-199A-5P	[32]
			MIP binds to the SH3 domain	[28]
MAP3K12	DLK	MKK3/6, MKK4/7	Inhibiting MAP3K12 mRNA transcription by overexpression Tetrachlorodibenzo-p-diox	[33]
			Phosphorylation activates MAP3K12	[34]
MAP3K13	LZK	MKK4/7	Increasing MAP3K13 mRNA transcription in autoimmune hepatitis	[35]
			Phosphorylation activates MAP3K13	[36]
MAP3K14	NIK	IKKα	Increasing NIK mRNA transcription by Glucocorticoids	[37]
			Inhibitors cause NIK conformational changes	[38]
			Ubiquitination activates NIK	[39]
MAP3K16	TAOK1	MKK3/6	Inhibiting TAOK1 mRNA transcription by captopril	[40]
			Phosphorylation activates TAOK1	[41]
MAP3K17	TAOK2	MKK3/6	Inhibiting TAOK2 mRNA transcription by miR-331-3p	[42]
			Phosphorylation activates TAOK2	[41]
MAP3K18	TAOK3	MKK3/6	Increasing TAOK3 mRNA transcription in high-fat diet mice	[43]
			Phosphorylation by leucine-rich repeat kinase 2	[44]
MAP3K19	RCK	MKK7	Increasing MAP3K19 mRNA transcription by oxidative stress	[45]
MAP3K20	ZAK	MKK4/7	Inhibiting ZAK mRNA transcription in liver cancer tissue	[46]
			Inhibitors cause ZAK conformational changes	[47]
			Phosphorylation activates ZAK	[48]
MAP3K21	MLK4	WNK1-SPAK	Inhibiting MAP3K21 mRNA transcription in liver cancer tissue	[49]
			MIP binds to the SH3 domain	[28]
A-Raf	/	MKK1/2	Increasing A-Raf mRNA transcription after hepatectomy in rats	[50]
			14-3-3 stabilized Raf dimerization	[18]
			Phosphorylation activates A-Raf	[51]

Table 1 (continued)

Gene name	Alternative name	Substrate	Examples of MAP3Ks activity regulation	Ref.
B-Raf	/	MKK1/2	Inhibiting B-Raf mRNA transcription peptide nucleic acid	[52]
			14-3-3 stabilized Raf dimerization	[18]
			Phosphorylation activates B-Raf	[51]
Raf-1	/	MKK1/2	Inhibiting of mRNA transcription after heat stimulation	[11]
			14-3-3 stabilized Raf dimerization	[18]
			O-GlcNAcylation stabilizes the expression of Raf1	[53]

immunodeficiency virus type 1 (HIV-1) and other viruses. This review summarizes recent advances in the field and enables the translation of the current relevant knowledge into therapeutic discoveries.

Mechanisms underlying the regulation of MAP3Ks activity

Upstream MAP4Ks, oxidative stress, inflammatory cytokines, medications, and pressure are the major activators of MAP3Ks. The unhindered signaling, defects in which are strongly linked to many disorders like cancer and inflammatory diseases, is determined by MAP3Ks activity. MAP3K regulates the level of its own activity through a variety of mechanisms, such as regulation of transcriptional abundance, allosteric regulation, and post-translational modification (Table 1).

The abundance of MAP3Ks is regulated at the transcriptional level, and its expression can be induced in a stimulus-dependent manner. MAP3K8 abundance is lower in cells not stimulated by VEGF-A, and it increases after stimulation. Continuous induction has the opposite effect, resulting in a decrease in MAP3K8 expression [24]. Similarly, the transcriptional levels of MAP3Ks are negatively regulated. The mRNA abundance of RAF1, MAP3K2, and MAP3K7 decreases as the temperature increases in heat-stimulated cells [11].

Some MAP3Ks can regulate kinase activity in another important way: allosteric regulation. A key event in RAF activation is RAF dimerization mediated by scaffold and chaperone 14-3-3. In addition, 14-3-3 binds to the catalytic domain of Apoptosis signal-regulating kinase-1 (ASK1) and inhibits its kinase activity [18].

MAP3Ks are phosphokinases; their post-translational modification, particularly phosphorylation, is critical for their activity regulation. The regulation of all MAP3Ks activities is mediated by phosphorylation. Autophosphorylation on Thr-575 activates MAP3K1 [60]. MAP3K2 and MAP3K3 are activated by lipopolysaccharide (LPS)-induced phosphorylation at MAP3K2 Ser-519 and MAP3K3 Ser-526, respectively [61]. Next to phosphorylation, ubiquitination is the most common post-translational modification of MAP3K. In the case of TNFα, MAP3K7 is polyubiquitinated by a Lys48 linkage at K72 and then degraded through the proteasome pathway [23]. An atypical E3 ligase zinc finger protein 91 primarily mediates the synthesis of the Lys63-linked ubiquitinated stabilizing protein, which allows MAP3K14 to activate itself [39]. In addition, MAP3K7 is acetylated to prevent self-phosphorylation and activation [62].

The several types of mechanisms underlying the regulation of MAP3Ks kinase activity make it possible to elicit suitable responses in various circumstances, including the antiviral innate immune response.

IFN-I signaling pathway

After virus infection, the host recognizes viral nucleic acid via different PRRs and activates different signaling pathways according to the type of nucleic acid [63, 64] (Fig. 1).

The RLR family can recognize viral RNA in the cytoplasm. RIG-I recognizes viral double-stranded RNA (dsRNA) and 5′-triphosphate-RNA, while melanoma differentiation-associated gene 5 (MDA5) recognizes long dsRNA. Laboratory of genetics and physiology 2 (LGP2) is mainly involved in the recognition and interaction of RNA with RIG-I and MDA5, but also in signal transduction [65]. Activated RIG-I and MDA5 interact with mitochondrial antiviral-signaling protein (MAVS); when stimulated by MDA5 or RIG-I CARD, MAVS oligomerizes and further recruits multiple tumor necrosis factor (TNF) receptor-associated factor (TRAF) proteins (such as TRAF2, TRAF3, and TRAF6), which are necessary for the activation of TANK-binding kinase 1 (TBK1) and inhibitor of nuclear factor kappa-B kinase ε (IKKε). Ultimately, these kinases phosphorylate interferon regulatory factor 3/7 (IRF3/7), which in turn leads to the production of IFN-I and interferon-stimulated genes (ISGs) [66–69].

TLRs are the most widely studied PRRs. Humans have ten different TLRs (TLR1–10), most of which can sense RNA viral infections [70]. TLR2 typically functions by forming heterodimers with other TLRs, such as TLR1 and

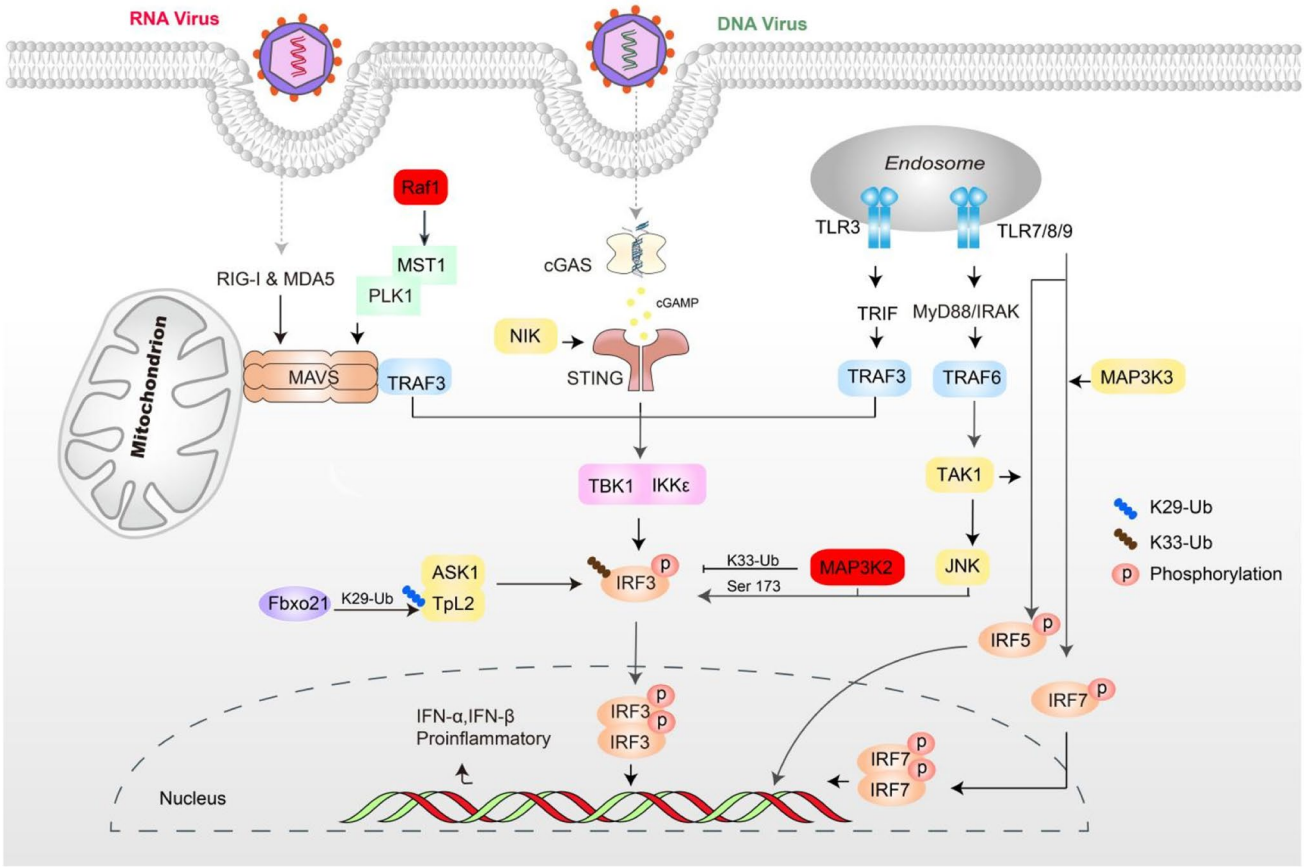

Fig. 1 MAP3Ks in the IFN-I pathway. When viral nucleic acids bind to pattern recognition receptors, the corresponding adaptor proteins are recruited to activate three major signaling pathways: RIG-I, cGAS-STING, and TLR. RIG-I binds to MAVS via caspase recruitment domain (CARD)-CARD interaction; cGAS recognizes DNA in the cytosol and is activated to produce cGAMP, which then binds to and activates STING; and TLR3 transmits signals via TRIF. These can activate the downstream protein kinase TBK1 and further phosphorylate IRF3/7. TLR7/8/9 recruit MyD88 and IRAK to form the MyD88 signaling complex, which can activate IRF5/7 and induce downstream IFN-I synthesis and related IFN-stimulating factors. MAP3Ks upregulate or downregulate the signaling are indicated in yellow and red backgrounds, respectively

TLR6, to sense virus proteins [71, 72]. In the endosomal compartment, TLR3 recognizes viral dsRNA [73], whereas TLR7/8 recognizes viral single-stranded RNA [74]. All TLRs, except TLR3, activate interleukin-1 (IL-1) receptor-associated kinases (IRAKs) through myeloid differentiation factor 88 (MYD88), which in turn activates TRAF6. TLR3 recruits TIR domain adaptor molecule 1 (TICAM-1, also known as TRIF) [75, 76]. IKK complex, NF-kappa-B essential modulator (NEMO), and TBK1 are activated after a series of signal transductions, and they further activate transcription factors such as IRF3/7 and NF-κB to promote the release of IFN-I and other inflammatory factors.

Viral DNA is primarily recognized by cyclic GMP-AMP (cGAMP) synthase (cGAS) [77]. cGAS then synthesizes cGAMP to deactivate stimulator of interferon genes (STING) on the endoplasmic reticulum, causing it to transfer to the Golgi apparatus, thereby activating the TBK1-IRF3 signaling axis and triggering the production of IFN-I and other inflammatory factors. Absent in melanoma 2 (AIM2) [78], dead-box helicase 41 (DDX41) [79], and TLR9 [64, 80], among others, can also sense viral DNA.

MAP3Ks in IFN-I signaling pathway

Many MAP3Ks affect the function of important IFN-I signaling molecules, thereby regulating IFN-I production (Fig. 1). Here, we focus on how a host can use MAP3Ks to regulate the IFN level for an antiviral immune response. Table 2 summarizes the list of MAP3Ks targeting key molecules in the main innate immune pathways mediated by RNA and DNA viruses.

Table 2 MAP3Ks targeting key molecules in IFN-I signaling pathway

Viruses	Host targets	MAP3Ks involved	Functions of MAP3Ks	Ref.
RNA virus				
HIV	MAVS	Raf-1	Inhibiting IFN production	[81]
	Unclear	MAP3K11	Facilitating antiviral responses	[82]
VSV	Unclear	Raf-1 and a-Raf	Inhibiting antiviral responses	[83]
	IRF3	MAP3K2	Inhibiting IFN production	[84]
	IRF3	ASK1	Enhancing IFN production	[85]
	Unclear	NIK	Enhancing IFN production	[86]
SeV	IRF3	MAP3K2	Inhibiting IFN production	[84]
	Unclear	ASK1	Enhancing IFN production	[87]
	IRF3	TPL2	Enhancing IFN production	[88]
IAV	Unclear	ASK1	Enhancing IFN production	[87]
EMCV	Unclear	ASK1	Inhibiting viral replication	[87]
NDV	Unclear	ASK1	Inhibiting viral replication	[87]
FMDV	IRF3	TPL2	Enhancing IFN production	[88]
LCMV	Unclear	NIK	Enhancing IFN production	[86]
HCV	Unclear	MAP3K11	Enhancing IFN production	[89]
DNA virus				
HSV-1	IRF3	MAP3K2	Inhibiting IFN production	[84]
	IRF7	MAP3K3	Enhancing IFN production	[90]
	IRF3	ASK1	Enhancing IFN production	[85]
	STING	NIK	Enhancing IFN production	[91]
MCMV	Unclear	TPL2	Enhancing IFN production	[92]
MHV-68	STING	NIK	Enhancing IFN production	[91]

Raf family

The Raf family is the most studied subfamily of MAP3Ks and includes A-Raf, B-Raf, and C-Raf (Raf-1), which selectively activate MAP2K1 and MAP2K2 [93, 94]. Raf-1 kinase is required for TLR8 and dendritic cell (DC)-specific intercellular adhesion molecule 3-grabbing non-integrin (DC-SIGN)-mediated signaling [95]. In addition, HIV-1 [96] and IFN-β [97] can activate Raf-1. In DCs, Raf-1 limits antiviral IFN-I responses during HIV-1 infection. Raf-1 depletion or pharmacological inhibition of Raf-1 with the small-molecule inhibitor GW5074 could induce the transient expression of IFN-β [81]. Mechanistically, Raf-1 activates mammalian sterile 20-like kinase 1 (MST1), which further phosphorylates polo-like kinase 1 (PLK1) at Thr210 and facilitates its interaction with MAVS, thus blocking MAVS-mediated signaling. In addition, there is an increased viral replication in A-Raf- or Raf-1-deficient cell lines during early vesicular stomatitis virus (VSV) infection [83]. This implies that A-Raf and Raf-1 are also involved in VSV-induced innate immunity.

MAP3K1

MAP3K1 is required for MAPK signal transmission by activating MAP2K1/4/7. MAP3K1 regulates the proliferation of invariant natural killer T cells and promotes the generation of T helper 2 (Th2) cytokines [98]; in addition, it is essential for B cell proliferation and antibody production [99]. Endogenous MAP3K1 is necessary for IFN-I production by cytoplasmic dsRNA [100]. Suppression of MAP3K1 substantially decreases poly(I:C)-induced IFN-β mRNA expression by inhibiting the activation of RIG-I and MAVS. Meanwhile, co-transfection of MAP3K1 and IRF3 synergistically increases IRF3-promoter activity. Real-time polymerase chain reaction analysis demonstrated that MAP3K1 knockdown with various siRNA oligonucleotides considerably lowers IFN-α/β levels. Mechanistically, MAP3K1 interacts with TRAF6, further stimulating the downstream IKK complex and MAP2Ks, thus playing a regulatory role in IFN-I production.

MAP3K2

MAP3K2 primarily transmits signals through MAP2K4/5/7 [101]. MAP3K2-regulated intestinal stromal cells are identified as a new type of intestinal mesenchymal stromal cells that depend on MAP3K2 to regulate intestinal stem cell ecology and protect against intestinal damage [102]. In addition, MAP3K2 is an effector of tumor cell-secreted epidermal growth factor receptor (EGFR) in macrophages, which reduces the host innate antiviral immunity [84]. MAP3K2 phosphorylates IRF3 at Ser173

without involving extracellular-signal-regulated kinase 5 (ERK5) or c-Jun N-terminal kinase (JNK), increases polyubiquitination via the K33-linkage, and inhibits virus-induced IRF3 dimerization and nuclear translation, which further reduces the production of IFN-β and IFN-stimulated genes. In addition, *Map3k2*-deficient mice are more resistant to viral infection and exhibit reduced viral loads compared to wild-type (WT) mice [84]. Even without the EGFR trigger, MAP3K2 modulates innate antiviral immunity by regulating its activity in different ways. However, further studies are required to better understand the underlying mechanisms.

MAP3K3

In addition to MAP3K2, MAP3K3 can also activate MAP2K5 [103] and regulate vascular malformations [104], kidney diseases [105], and immune activation [106]. Following the cellular activation of the TLR7/9 signaling pathway to induce various types of IFN-Is, MAP3K3 is a potent stimulator of IRF7. Most notably, IRF7, induced by IFN-Is, is a key regulator of virus-driven IFN-I production [107]. MAP3K3 overexpression strongly activates IRF7, resulting in the induction of IFN-Is, whereas TLR7/9 ligand activation results in decreased innate immune responses in cells lacking MAP3K3. Interaction between MAP3K3 and IRF7 induces interferon production, which results in IRF7 phosphorylation at multiple sites [90]. In vivo, MAP3K3 knockdown reduces IFN-I induction and increases the susceptibility to herpes simplex virus type 1 (HSV-1) infection. Endogenous MAP3K3 binds to and phosphorylates IRF7 upon the binding of TLR9 to its specific ligand CpG DNA. These findings implicate the existence of crosstalk between MAP3K activation and IFN-I induction in the endosomal TLR pathway.

MAP3K5 (ASK1)

MAP3K5 (also known as apoptosis signal-regulating kinase 1; ASK1), MAP3K6 (ASK2), and MAP3K15 (ASK3) are the commonly known members of the ASK family. ASK1, the most studied of the three ASKs, regulates cell survival primarily via the MAP2K3/6-JNK and MAP2K4/7-p38 pathways. ASK2 is extremely similar to ASK1, especially in its kinase domain, and forms a heterologous complex with ASK1, which is necessary for the stability and activity of the ASK2 protein. Therefore, ASK2 functions only as a MAP3K when ASK1 is present [21, 108]. In addition, ASK3 plays a significant role in both osmotic shock and stress [109]. ASK1 not only mediates oxidative stress signaling but also plays a role in innate immunity. ASK1 knockdown in mice enhances the propagation of influenza A virus (IAV), a member of the *Orthomyxoviridae* family, and reduces IFN-I production in the lungs. Additionally, the increase in IFN-β mRNA abundance in response to encephalomyocarditis virus (EMCV) and newcastle disease virus (NDV) infections was blocked by ASK1 knockdown [87]. This emphasizes the importance of ASK1 as an antiviral protein in vivo. In contrast, ASK2 is required for ASK1-dependent apoptosis but not for induction of IFN-β expression. Furthermore, IAV replication in the lungs is increased in mice with ASK1 or ASK2 gene deletions. Therefore, ASK1/2 is involved in antiviral defense mechanisms; however, ASK2 is a critical regulator of apoptosis rather than IFN-I responses.

Proinflammatory cytokines, including IL-1, IL-6, and TNF-α, are also produced via the RLR pathway. These cytokines regulate the permeability of the endothelium, which lines blood arteries and recruits blood cells and plasma proteins to infection sites. $ASK1^{-/-}$ macrophages infected with the virus display lower levels of IL-6, suggesting the involvement of ASK1 in the induction of these inflammatory cytokines [87].

F-box-only protein 21 (Fbxo21) plays a critical role in regulating the innate antiviral response by facilitating Lys29-linkage and activating ASK1. ASK1 without the Lys29-linkage cannot rescue the innate antiviral response in $Map3k5^{-/-}$ RAW264.7 cells, suggesting that Fbxo21-mediated ubiquitination and ASK1 activation are required for the innate antiviral responses [85].

MAP3K7 (TAK1)

MAP3K7 (also known as transforming growth factor-β-activated kinase 1, TAK1) is a key factor mediating the signal transduction of IL-1 [90], transforming growth factor-beta (TGF-β) [110, 111], and TLRs [112]. IRF3 is the true substrate of JNK, and upstream kinase TAK1 promotes the phosphorylation of IRF3 by JNK [113]. JNK1/2 can directly catalyze the phosphorylation of Ser173 in IRF3. Co-expression of TAK1 significantly increases the activity of this kinase. However, TAK1 cannot directly phosphorylate IRF3.

TAK1 inhibition results in a slight decrease in IFN-β levels after poly(I:C) treatment of WT bone marrow-derived macrophages (BMDMs); however, the difference is not statistically significant [114]. Treatment with TAK1 inhibitors significantly reduces IFN-β induction after poly(I:C) stimulation in $IRAK1^{-/-}$ and $IKK\varepsilon^{-/-}$ BMDMs compared to that in DMSO-treated $IRAK1^{-/-}$ and $IKK\varepsilon^{-/-}$ BMDMs. These findings imply that the enzymatic activity of TAK1 is important for regulating IFN-I responses downstream of TLR3 by IRAK1.

MAP3K8 (TPL2)

MAP3K8 (tumor progression locus 2; TPL2) is functionally similar to MAP3K1 in the MAPK cascade signal, but, in most cases, its function does not involve the activation of MAP2K7 [115]. The TPL2-ERK signaling pathway and TLR 2/4/7 directly activate the inflammatory axis and positively regulate ERK phosphorylation and early TNF secretion [116]. In addition, TPL2 positively regulates p38α and p38δ in neutrophils [117]. TPL2 regulates IFN activation through IRF3, which leads to increased replication of foot-and-mouth disease virus (FMDV) [88]. However, IFN-α, myxovirus resistance 2, and CXC motif chemokine ligand 10 expression are significantly reduced in *Tpl2*-deficient mice, with no detectable change in IRF3 phosphorylation. FMDV capsid protein VP1 inhibits TPL2 phosphorylation at Thr290, a critical functional site of TPL2 that promotes IRF3-mediated activation of the IFN-β signaling pathway. Similar results are obtained when cells are stimulated with poly(I:C) and Sendai virus (SeV) instead of FMDV.

The MAP3K8 (*Sluggish*) mutation causes splicing errors in the *Map3k8*-encoded Tpl2 transcript. MAP3K8$^{Sluggish/Sluggish}$ mice are resilient to mouse cytomegalovirus (MCMV) infection but extremely susceptible to group B streptococcus infection [92]. CpG-B-induced IFN-I production is significantly reduced in peritoneal macrophages isolated from homozygous MAP3K8$^{Sluggish/Sluggish}$ mice, whereas LPS- and poly(I:C)-induced IFN-I production remains unaffected. Thus, TPL2 is important for IFN-I production in peritoneal macrophages, especially in response to MyD88-dependent TLR signaling.

MAP3K14 (NIK)

MAP3K14 (also known as NF-κB-inducing kinase, NIK) is a helpful regulator of the DNA virus-activated cGAS-STING pathway [91]. STING and NIK colocalize and interact with each other. NIK relies on its kinase activity and functions in concert with STING to boost IFN-β transcription [91]. NIK dysfunction has serious consequences for pro-immune activation during lymphocytic choriomeningitis virus (LCMV) and vesicular stomatitis virus (VSV) infections. Indeed, viral replication is reduced in the spleen tissue of WT and *Map3k14*$^{aly/aly}$ mice after infection with either virus strain, and serum IFN levels are considerably reduced [86]. The *aly* mutation results in an amino acid substitution (G855R) in the Nik code. *Aly/aly* mice are completely devoid of lymph nodes and Peyer's patches, thus, they are highly susceptible to viral infections [86, 118]. NIK suppresses hepatitis C virus (HCV) replication in Huh-7 cells [119]. In addition, NIK is a component of the NF-κB-inducing signaling cascade, independent of any specific MAPK cascade [120].

Other MAP3Ks

Following a systematic evaluation of multiple genomic datasets, RNA interference (RNAi) screening tests demonstrated that MAP3K11 deletion drastically lowers RIG-I signaling-mediated IFN production [89]. Increased HIV-1 transcription by MAP3K11 is dependent on its kinase activity, and the corresponding MAP3K11 siRNA reduces HIV-1 infection by 40% [82].

Several MAP3Ks that regulate IFN-I signaling have been identified; however, each host MAP3K has a unique set of functions that vary depending on the virus and cell type. Further research is required to determine the antiviral roles of MAP3Ks in IFN-I signaling.

NF-κB signaling pathway

NF-κB is a major transcriptional regulator in antiviral immunity and is activated after viral infection. In the previous chapters, we mentioned that after viral nucleic acid is recognized by PRR, the NF-κB pathway can be effectively activated, but it is not complete. Here, we introduce in detail two NF-κB pathways that play key roles in cells: the canonical NF-κB pathway and the non-canonical NF-κB pathway. Interestingly, these two pathways are dominated by two respective MAP3Ks (Fig. 2) [121, 122].

In the canonical NF-κB pathway, MAP3K7, also known as TAK1, occupies a dominant position. After the viral nucleic acid binds to the TLR, TAK1 is activated. TAK1 is an upstream kinase that activates the IKKα, IKKβ, and NEMO complex. The phosphorylation of inhibitor of NF-κB (IκB) by IKK occurs on two serine residues, and proteasomal degradation occurs, resulting in NF-κB dimers (including RelA/p50) being rapidly released. Eventually, the constitutively activated dimer translocates to the nucleus where it induces the transcription of NF-κB target genes [123].

Activation of the non-canonical NF-κB pathway is dependent on another MAP3K: NIK. Activated NIK phosphorylates the IKK complex, which is notable for containing only two IKKα subunits. Upon activation, IKKα directly phosphorylates p100, leading to the processing of p100 into p52 and, finally, nuclear translocation of the RelB-p52 heterodimer [124].

It is noteworthy that both DNA virus and RNA virus can activate NF-κB transcription in two ways. This will be elaborated in the next chapter.

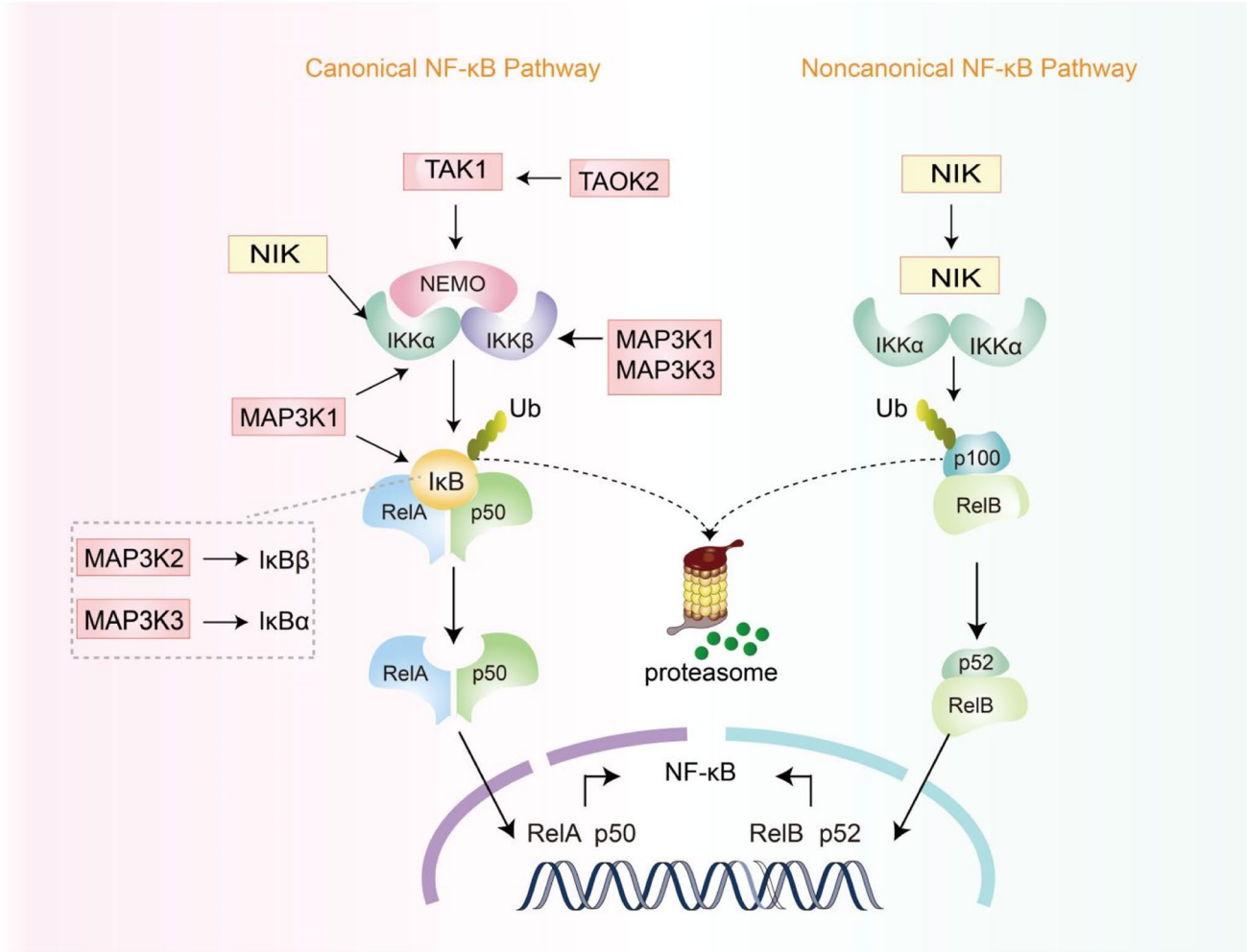

Fig. 2 MAP3Ks in the NF-κB pathway. Canonical NF-κB pathway: TAK1 phosphorylates and activates the NEMO-IKKα-IKKβ complex, and the activated IKKβ targets IκB for proteasomal degradation, thereby translocating p50-RelA to the nucleus and inducing NF-κB transcription. Non-canonical NF-B pathway: NIK phosphorylates and activates IKKα, and then recruits IKKα to p100, which then phosphorylates and degrades p100 by the proteasome. Finally, p52 bound to RelB is translocated to the nucleus to regulate the transcription of NF-κB. Through phosphorylation of the IKKα subunit, NIK also promotes canonical NF-κB pathway activation

MAP3Ks in NF-κB signaling pathway

TAK1 and NIK are the main kinases mediating the two NF-κB pathways, while other MAP3Ks still play a role in NF-κB signal transduction. Interestingly, many viruses can activate two NF-κB pathways in different ways, which has nothing to do with whether it is a DNA or RNA virus. Here, we not only outline how other MAP3Ks mediate NF-κB signaling (Fig. 2) but also elaborate on how the host regulates NF-κB activity through MAP3Ks after virus invasion, and then exerts antiviral effects (Table 3).

The phosphorylation and subsequent proteolysis of IκB is an important mechanism for NF-κB activation. MAP3K1 transfection causes IκB degradation and activates NF-κB [137]. In addition, MAP3K1 participates in NF-κB signaling by activating IKKα/β [138]. MAP3K3 and MAP3K2 regulate the formation of IκBα:NF-κB and IκBβ:NF-κB complexes [139]; MAP3K3 can also phosphorylate Ser177 and Ser181 sites in IKK2 (IKKβ) [140]. Interestingly, thousand and one-amino acid protein kinase 2 (TAOK2), another MAP3K, inhibits the TAK1-mediated activation of IKKα [141].

TAK1 plays a crucial role in HIV-1 infection; it increases HIV-1 replication by modifying NF-κB signaling. Viral protein R (Vpr), produced by HIV-1, stimulates the association between TAK1 and TAK1-binding protein 3 (TAB3), as well as TAK1 polyubiquitination and phosphorylation. This in turn activates NF-κB and increases long terminal repeat (LTR)-dependent viral gene expression. Activation of HIV-1 LTR promoter by Vpr is reduced when TAK1 expression is knocked down [125]. Transmembrane glycoprotein gp41 (gp41CD) of both HIV and Simian

Table 3 Virus targeting key MAP3Ks in NF-κB signaling pathway

Viruses	Virus protein	MAP3Ks involved	Signaling Function	Ref.
RNA virus				
HIV	Vpr	TAK1	Inhibiting NF-κB signaling	[125]
	gp41	TAK1	Activating NF-κB signaling	[126]
	Tat	NIK	Activating NF-κB signaling	[127]
SARS-CoV-2	N	TAK1	Activating NF-κB signaling	[128]
	NSP6	TAK1	Activating NF-κB signaling	[129]
	ORF7a	TAK1	Activating NF-κB signaling	[129]
RSV	Unclear	TAK1	Activating NF-κB signaling	[130]
	Unclear	NIK	Activating NF-κB signaling	[131]
SIV	gp41	TAK1	Activating NF-κB signaling	[126]
DNA virus				
HBV	HBsAg	TAK1	Inhibiting NF-κB signaling	[132]
		NIK	Activating NF-κB signaling	[133]
HSV-1	Unclear	TAK1	Activating NF-κB signaling	[134]
	Unclear	NIK	Activating NF-κB signaling	[134]
HSV-2	Us2	TAK1	Activating NF-κB signaling	[135]
EBV	LMP1	NIK	Activating NF-κB signaling	[136]

immunodeficiency virus (SIV), which is crucial for viral replication, activates NF-κB via TAK1 [126]. Sterile α motif and histidine-aspartate domain-containing protein 1 (SAMHD1), an HIV-1 restriction factor, prevents TAK1 phosphorylation, thereby inhibiting the transcription of NF-κB and HIV-1 replication [142], in VSV glycoprotein-pseudotyped single-cycle HIV-1. This demonstrates the restrictive role of SAMHD1 in preventing the viral protein activation of NF-κB.

NF-κB is crucial to the immunological response to HSV infection; however, the mechanism underlying the activation of NF-κB by HSV remains unclear. Alternative kinase activities cannot be ruled out; however, inactivation of TAK1, MAP3K1, or NIK mutants decreases NF-κB activation during HSV infection [134]. In addition, phosphorylation of the three MAP3Ks is elevated during HSV infection. Lu et al. [135] screened for the unique short (Us) region of HSV-2, revealing that HSV-2 Us2 activates NF-κB signaling. Specifically, Us2 interacts with TAK1 to activate TAK1 and downstream genes, thereby activating NF-κB. In mice, Us2 also increases the phosphorylation of TAK1, IKKβ, and IκB.

Severe acute respiratory syndrome-associated coronavirus 2 (SARS-CoV-2), the cause of an active pandemic, stimulates NF-κB and causes the release of numerous inflammatory factors, through its nucleocapsid (N) protein. TAK1 and IKK complexes are attracted to and activated following the liquid-liquid phase separation of the N protein, which in turn triggers the transcription of NF-κB [128]. Another study showed that nonstructural protein 6 (NSP6) and open reading frame 7a (ORF7a) of SARS-CoV-2 interacted with TAK1 dependent on their own ubiquitination, and knockout of TAK1 eliminated NSP6 and ORF7a at the activation of NF-κB [129].

Several other viruses can modify the activation state of NF-κB via TAK1. Hepatitis B virus (HBV) mRNA is translated into hepatitis B surface antigen (HBsAg), which specifically binds to TAK1 and TAB2 and prevents TAK1 phosphorylation, thus inhibiting activation of the NF-κB signaling pathway and evading immune system detection [132]. After viral infection, upregulated TAP1 binds to TAK1 and prevents NF-κB signaling. TAK1 boosts NF-κB activation induced by the respiratory syncytial virus (RSV) [130]. Collectively, TAK1 regulates NF-κB signaling following viral infection, suggesting its potential as a viable therapeutic target for associated viral infections.

Viral infection is significantly impacted by NF-κB signaling, which is mediated by NIK. HIV-1 Tat protein promotes NF-κB activation and accelerates IκB degradation through NIK [127]. RSV infection enhances NIK expression and promotes interactions among NIK, IKK, and p52, which strengthens NF-κB activation [131]. The reduction in nuclear accumulation of p52 and blocking of RSV processing of p100 by NIK knockdown indicates that NIK is crucial for RSV-induced NF-κB activation. In addition, nuclear localization of NIK is essential for HBV-induced NF-κB activation [133]. Nuclear localization signal (NLS)-containing NIK is imported into the nucleus after IFN-γ treatment; however, NLS-free NIK remains in the cytoplasm, suggesting that IFN-γ suppresses NF-κB activation by promoting NIK accumulation in the nucleus. Latent infectious membrane protein 1 (LMP1) of the Epstein-Barr virus (EBV) activates NF-κB through its C-terminal activation domains 1 and 2 (CTAR1 and

CTAR2). First, CTAR1 specifically recruits TRAF3 and NF-κB via NIK- and IKKα-induced p100 processing. Subsequently, CTAR2 preferentially recruits TRAF6, which activates the IKKα/β/γ complex after activating TAK1, and phosphorylates and degrades IκBα, eventually leading to NF-κB activation [136].

Therefore, NF-κB signaling is critically dependent on the regulatory mechanisms of MAP3Ks during the viral infection cycle. After infecting host cells, viruses manipulate MAP3K activity in various ways, thereby altering NF-κB signaling and affecting antiviral immunity. Exploring new therapeutic strategies targeting MAP3K to inhibit viral replication and disease pathogenesis requires elucidating virus-MAP3K-NF-κB interactions.

MAP3K family: a potential target for antiviral therapies

MAP3Ks provide prospective therapeutic targets for the widespread diagnosis and treatment of viral infections owing to recent developments in our understanding of the function of MAP3Ks in controlling antiviral immune signals. According to this review, it is not difficult to find that MAP3Ks play a key role in HIV-1 virus infection. In addition, MAP3Ks-related inhibitors were shown to have the perfect mechanism for the treatment of HIV-1-related diseases. Therefore, targeting MAP3Ks may lead to the development of effective drugs against HIV-1 infection and related diseases, which we summarized in detail. Moreover, MAP3Ks have also been targeted for the treatment of other viruses with good results.

MAP3Ks as a therapeutic strategy for HIV-1-related diseases

The HIV-1 epidemic is a public health crisis in countries and regions worldwide, even though antiretroviral therapy has greatly reduced the infection rate of HIV-1 and prolonged the lives of HIV-1 patients [143]. Some patients still show HIV-1-associated neurocognitive disorder (HAND), which greatly affects the quality of their lives. Studies have pointed out that HIV-1 proteins, gp120 and Tat, activate Mixed lineage kinase 3 (MLK3) in neurons, leading to the death of neurons and the production of inflammatory factors with neurotoxic effects. Furthermore, either kinase inactivation or the pharmacological inhibition of MLK3 activity protects neuronal survival, suggesting that MLK3 activity may determine the development of HAND [144, 145]. Bodner et al. [146] first discovered that the first-generation MLK inhibitor CEP-1347 dose-dependently protects hippocampal neurons from HIV-1 gp120-induced neurotoxicity. However, Bodner et al. studied only gp120, a neurotoxin, on a single hippocampal neuron; Sui et al. [144] further found that HIV-1 gp120 and Tat can also cause microglial apoptosis by activating MLK3. Interestingly, CEP-1347 treatment also prevented the activation of gp120 and Tat in monocytes. In 2010, Eggert et al. [147] further verified the neuronal protective effect of CEP-1347 in models of NeuroAIDS. These results all suggest that inhibiting MLK3 is a potential strategy for the treatment of HAND. Regrettably, due to the structure of CEP-1347, it is not conducive to the penetration of the blood-brain barrier, which led to its failure to show efficacy during Phase II clinical trials for the treatment of Parkinson's disease. In addition, the poor pharmacokinetic and metabolic characteristics have become evidence that CEP-1347 has no efficacy [148]. A novel MLK3 inhibitor, URMC-099, has been shown to protect microglia from phagocytosis, lowers inflammation induced by HIV-1 Tat protein, and reduces HAND-associated symptoms [149] (Fig. 3A). In addition, it has also been shown that URMC-099 reverses HIV-1 Nef protein-mediated sequestration of transcription factor EB in the cytoplasm, induces autophagy and lysosomal biogenesis, and encourages the accumulation of co-administered, nano-formulated antiretroviral medication in persistently infected macrophages [145] (Fig. 3B).

Chronic kidney disease is a common condition among patients with HIV-1, and HIV-1-associated nephropathy (HIVAN) rapidly leads to kidney failure. The ASK1 inhibitor, GS-444217 significantly inhibits ASK1 and downstream MAPK activation. Treatment with GS-444217 reduces HIVAN-associated damage and improves renal function. Therefore, targeting ASK1 is promising for the development of novel treatments against HICAN (Fig. 3C) [150].

MAP3Ks as a therapeutic strategy for other virus-related diseases

The coronavirus disease 2019 epidemic is a global health challenge, and it is a long and complicated process to redevelop drugs to market. Drug repurposing was mentioned as an effective solution against SARS-CoV-2 (Fig. 4) [151].

Vemurafenib and PLX-4720 are inhibitors of the B-Raf mutation V600 [152, 153]. Vemurafenib interacts with the nucleotide-binding domain of the cell surface protein BiP, thus limiting viral replication by neutralizing viral binding [154]. In contrast, in another study, vemurafenib caused a time-dependent increase in the expression of angiotensin-converting enzyme 2 (ACE2), which may contribute to SARS-CoV-2 infection [155]. PLX-4720 interacts with receptor-interacting serine/threonine-protein kinase 1 (RIPK1) during SARS-CoV-2 infection [153]. RIPK1 is

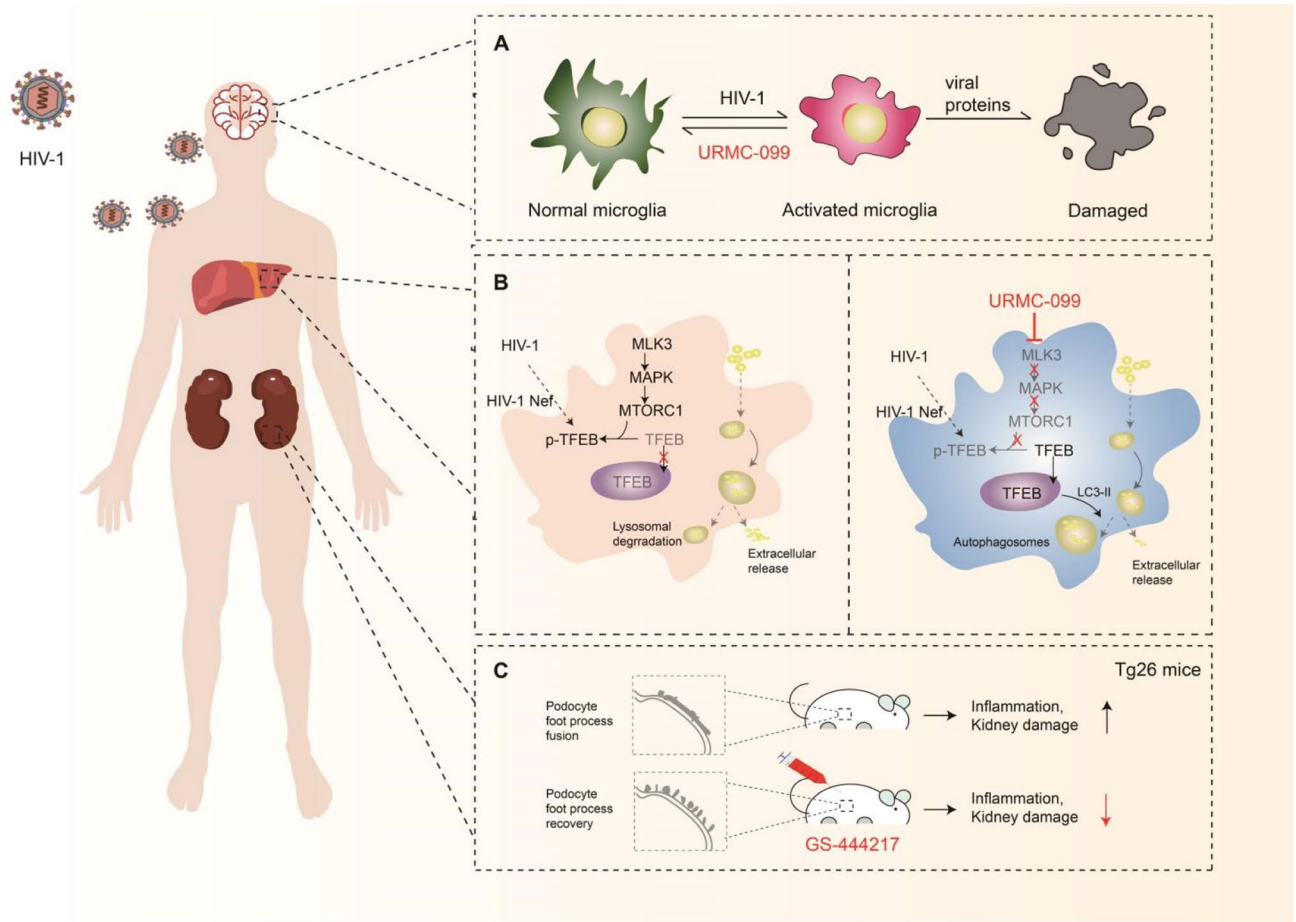

Fig. 3 Schematic representation of a working model of drugs against HIV-1-related diseases. **A** Following HIV-1 infection, microglia activate and retract their branches. The action of HIV-1 viral proteins eventually leads to synaptic dendrite damage and cell death. **B** Following HIV-1 infection, HIV-1 Nef protein sequesters transcription factor EB (TFEB) in the cytoplasm and inhibits lysosomal biogenesis and autophagy, thus preventing nanoART from accumulating in the cells and eventually leading to viral replication. Both these phenomena are suppressed by the administration of URMC-099. **C** Treatment with an ASK1 inhibitor recovers the fused podocyte foot process and elevated inflammatory cytokines levels, in the HIVAN mice model. MTORC1, the mechanistic target of rapamycin complex 1; LC3, light chain 3

activated by nsp12 and regulates the expression of ACE2 to promote viral transmission. SARS-CoV-2 enters the human body via the ACE2 receptor, and its high expression increases the body's susceptibility to SARS-CoV-2. Sorafenib and another multikinase inhibitor, regorafenib, also exert antiviral efficacy [156, 157], and anti-SARS-CoV-2 activity. Sorafenib can decrease the activity of the nidovirus RdRp-associated nucleotidyltransferase domain (NiRAN) of SARS-CoV-2 RdRp by interacting with the aspartate residue of the anticipated active site [158, 159]. Regorafenib represents a potential drug candidate for blocking the interaction between the viral receptor-binding domain S1 and ACE2 [160]. Another Raf inhibitor, Dabrafenib, was found to inhibit SARS-CoV-2 infection in vitro [161, 162]. Collectively, these drugs may be rapidly applied to the clinical treatment of SARS-CoV-2, but their specific mechanisms are still unknown.

EBV expresses latent membrane protein 1 (LMP1), and LMP1-transgenic mice exhibit hyperproliferation of oncogenic cells, inflammation, or malignancies. Effective treatment of EBV-related tumors requires an understanding of LMP1 network signaling [163, 164]. LMP1 activates TPL2 via IKK2 and causes TPL2 phosphorylation, thus activating JNK. When treated with the TPL2 inhibitor, TC-S7006, the capacity of LMP1 to activate JNK is lost, leading to the death of LMP1-dependent cancer cells [164]. Therefore, TPL2 is a potential new target for EBV-induced cancers.

Acute respiratory distress syndrome (ARDS) and pneumonia may be caused by H5N1 viral infection, which is a highly pathogenic avian influenza A virus, that disrupts the alveolar epithelial barrier [165]. Specifically, the H5N1 virus stimulates the expression of the E3 ubiquitin ligase Itch by activating TAK1 and downstream MAPKs. TAK1 knockdown or the use of TAK1 inhibitors restores the

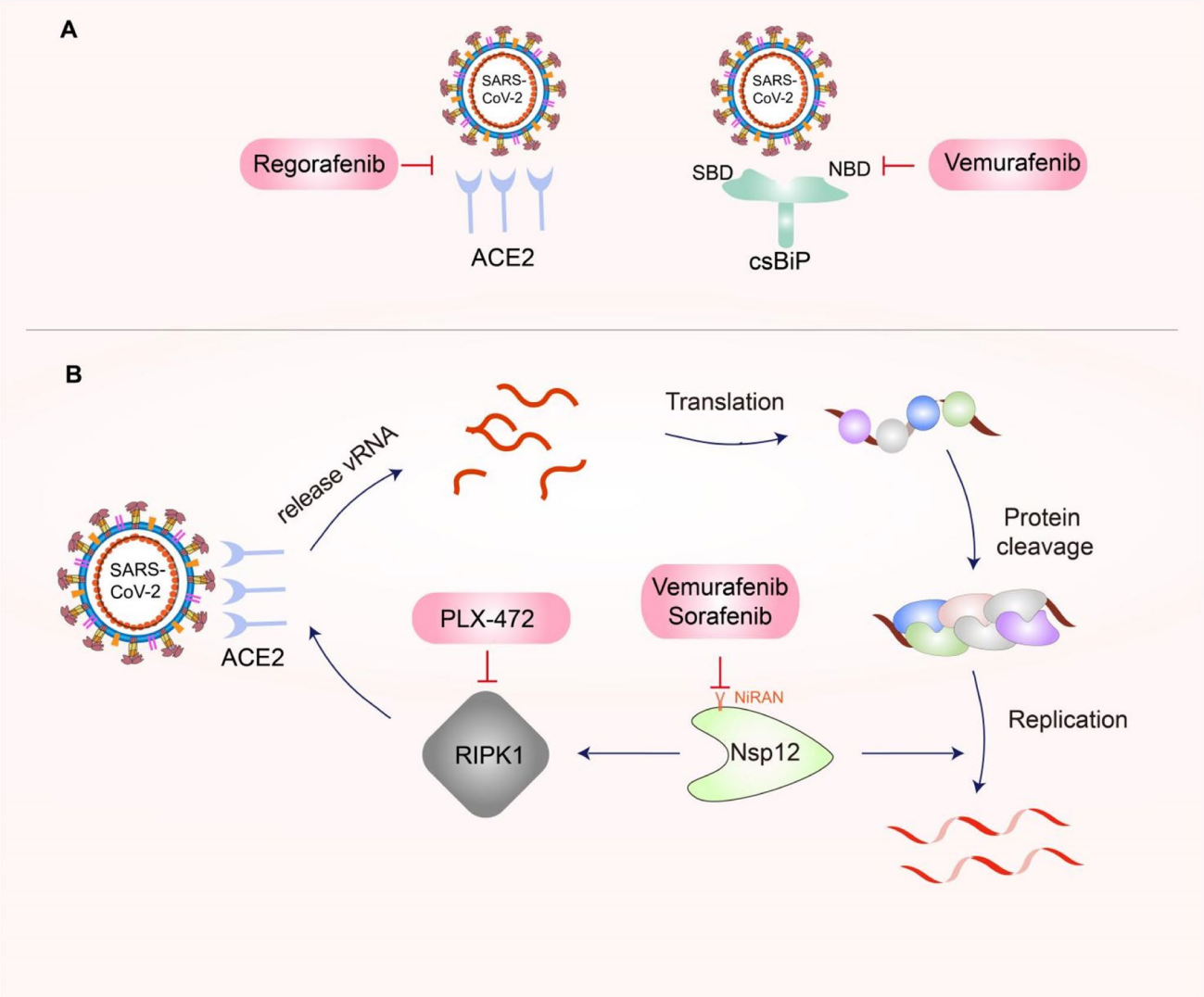

Fig. 4 Schematic representation of two working models of anti-SARS-CoV-2 drugs. **A** Inhibiting the virus–host combination prevents viral invasion and achieves an antiviral effect. **B** Inhibiting relevant targets of the transduction pathway of SARS-CoV-2 prevents viral invasion and achieves an antiviral effect. SBD, substrate-binding domain; NBD, nucleotide-binding domain; csBIP, cell surface binding immunoglobin protein

expression levels of occludin alveolar junction proteins, which were ubiquitinated and degraded [166]. Thus, TAK1 suppression could provide a target for the development of anti-H5N1 viral infection measures [166].

MAP3Ks offer a therapeutic window for antiviral treatment and MAP3K regulation is a possible antiviral therapeutic approach (Table 4). However, there are some issues to be addressed. RAF inhibitors have the potential to suppress SARS-CoV-2 infection; however, RAF-MAPK is a crucial component of the body's perception of external pressure stimuli. TPL2 and TAK1 are essential for NF-κB signaling; however, their inhibition could compromise the immune system and facilitate additional infections. Therefore, the negative effects of MAP3K inhibition require careful evaluation.

Discussion and perspectives

MAPKs, not just MAP3Ks, play an important role in regulating IFN-I production. MAP4K1 inhibits IFN-I production by targeting TBK1/IKKε [175], while p38 MAPK reportedly inhibits STING activation by increasing phosphorylation of USP21 at Ser538, thus further controlling the IFN-I pathway [176]. JNK activation is crucial for the proper functioning of the IFN-I pathway [113, 177]. These findings underscore the importance of MAPKs in IFN-I production and could lead to the discovery of new antiviral targets.

MAP3Ks inhibitors are effective against HIV-1 infection and related diseases, and numerous MAP3Ks play vital roles against SARS-CoV-2 and other viruses. An in-depth understanding of

Table 4 MAP3KS inhibitors as antiviral strategies

Inhibitors	Target	Functions as an antiviral drug	Ref.
GS-44217	ASK1	Reducing HIVAN-associated damage and improving renal function	[150]
5Z-7-oxozeaenol	TAK1	Inhibiting porcine epidemic diarrhea virus replication	[167]
		Inhibiting H5N1 virus replication	[166]
TC-S7006	TPL2	Inhibiting LMP-1 activation of JNK	[164]
CEP-1347	MLK3	Inhibiting HAND progression	[144, 146, 147]
URMC-099	MLK3	Inhibiting HAND progression	[145, 149]
Vemurafenib	BRAF	Inhibiting Enterovirus A71 replication and assembly	[168]
		Inhibiting IAV-induced signaling activation	[169]
		Inhibiting virus and host binding	[154]
		Increasing ACE2 expression	[155]
Sorafenib	BRAF, RAF-1	Inhibiting the activity of NiRAN in SARS-CoV-2	[158]
		Inhibition of Rift Valley fever virus virion release from cells	[170]
		Inhibiting human cytomegalovirus replication	[171]
		Inhibiting replication of Eastern equine encephalitis viruses, Sindbis virus, and chikungunya virus	[172]
		Altering HCV entry steps and virion production	[173]
Dabrafenib	BRAF, RAF-1	Binding the inactive site of dengue virus NS3 protease	[174]
		Inhibiting LCMV virus replication	[161]
		Inhibiting SARS-CoV-2 virus replication	[161, 162]
Regorafenib	BRAF, RAF-1	Inhibiting the binding of SARS-CoV-2 S1 to ACE2	[160]
PLX-4720	BRAF	Inhibiting SARS-CoV-2 virus replication by RIPK1	[153]

the functions of MAP3Ks in the innate immune response is critical to prevent and treat virus-related illnesses. Targeting the MAP3K family of proteins is a promising therapeutic strategy for treating viral infections and associated diseases. Future research should focus on determining the antiviral mechanisms of existing drugs and translate new research findings into antiviral drug development strategies. We believe that elucidating MAP3Ks-virus interactions will resolve the current challenges and improve human health; this is supported by the comprehensive list references reviewed here.

Author contribution Jizhong Guan and Yao Fan performed the literature search and data analysis; Shuai Wang and Fangfang Zhou drafted and critically revised the work.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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