Review

Negative regulation of TBK1-mediated antiviral immunity

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ABSTRACT

TANK-binding kinase 1 (TBK1) plays pivotal roles in antiviral innate immunity. TBK1 mediates the activation of interferon regulatory factor (IRF) 3, leading to the induction of type I IFNs (IFN-α/β) following viral infections. TBK1 must be tightly regulated to effectively control viral infections and maintain immune homeostasis. TBK1 activity can be regulated in a variety of ways, such as phosphorylation, ubiquitination, kinase activity modulation and prevention of functional TBK1-containing complexes formation. Furthermore, multiple viruses have evolved elaborate strategies to circumvent IFN responses by targeting TBK1. Here we provide an overview of TBK1 in antiviral immunity and recent developments on the regulation of TBK1 activity.

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1. Introduction

TRAF family member-associated NF-κB activator (TANK)-binding kinase 1 (TBK1), also known as NF-κB-activating kinase (NAK) or T2K, is one of two non-canonical IκB kinases (IKKs) implicated in regulating the activation of IFN regulatory factor 3 (IRF3) and NF-κB signaling pathways. TBK1 was originally identified as a kinase that mediated TANK's ability to activate NF-κB [1]. TBK1 is an 84 kDa, 729-amino acid protein containing an N-terminal kinase domain, an ubiquitin like domain and two C-terminal coiled-coil domains [1]. As a non-canonical IKK, TBK1 is structurally similar to IKKε (another IKK-related kinase) and the canonical IKKs, IKKα and IKKβ [1–4]. The canonical IKKs and the IKK-related kinases could regulate each other by an intricate network involving phosphorylation of their catalytic and regulatory subunits to balance their activities during innate immunity [5]. Once activated, TBK1 and IKKε phosphorylate IKKα/β, decreasing the activity of the canonical IKK complex [5]. On the other hand, IKKα/β phosphorylate and directly activate TBK1 and IKKε [5].

TBK1 could induce IκB degradation and NF-κB activity through IKKβ [1,2]. However, studies with TBK1 and IKKε single-null and double-null mice did not observe a deficiency in NF-κB activation [6,7]. Therefore, the function of TBK1 in NF-κB activation remains controversial and needs to be further investigated. Although the role of TBK1 in the NF-κB pathway is controversial, its role in IRF3 activation and antiviral immunity is convincing. TBK1

coordinates with IKKε to phosphorylate transcript factors IRF3 and IRF7, leading to the induction of type I IFN (IFN-α/β) [6–10]. Although TBK1 and IKKε have indistinguishable activities in inducing type I IFN expression and subsequential antiviral responses, they do not seem to be redundant and exhibit differential expression patterns and substrates specificity [8,11]. TBK1 is ubiquitously expressed, whereas IKKε expression is restricted to particular tissue compartments and expressed at low basal levels in immune cells [2,11,87].

In this review, we will summarize the fundamental role of TBK1 in antiviral immunity and recent developments on the regulation of TBK1 activity.

2. TBK1 in antiviral immunity

The production of type I IFN is a fundamental cellular response to combating viral invasion [12,13]. Various virus structural components, including viral DNA, double stranded RNA (dsRNA), single-stranded RNA (ssRNA), and surface glycoproteins, are recognized as pathogen-associated molecular patterns (PAMPs) by pattern recognition receptors (PRRs) expressed in multiple immune cells. Among these PRR members, TLR3 [14], retinoic acid-inducible gene-I (RIG-I; also known as DDX58) [15–17], melanoma differentiation-associated gene 5 (MDA5; also known as IFIH1) [18], nucleotide-binding oligomerization domain protein 2 (NOD2) [19], RNA polymerase III (RNA pol III) [20,21], DNA-dependent activator of IFN-regulatory factors (DAI; also known as ZBP1) [22], IFNγ-inducible protein 16 (IFI16) [23,24], DNA-dependent protein kinase (DNA-PK) [25] and several DExD/H-box helicase superfamily members (DDX41 [26], DDX1–DDX21–DHX36 complex [27],)

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utilize TBK1 to activates downstream signaling transduction. These PRRs recruit different adaptors including TLR/IL-1R domain-containing adaptor protein inducing IFN-β (TRIF), mitochondrial antiviral signaling protein (MAVS, also called IPS-1, Cardif, or VISA) and stimulator of IFN genes (STING; also known as MITA, MPYS and ERIS) to activate TBK1 (Fig. 1). Activated TBK1 then phosphorylates IRF3 and IRF7, triggers their dimerization and nuclear translocation, where they form active transcriptional complexes that bind to IFN stimulation response elements (ISRE) and activate type I IFN genes expression [28]. Secreted type I IFN binds to IFN α/β receptor (IFNAR) and triggers the production of numerous anti-viral genes through the JAK/STAT pathway [29].

Besides its function in TBK1–IRF3 signaling pathways, TBK1 participates in the regulating of autophagy [30–32]. Autophagy is an evolutionarily conserved process of the eukaryotic cell and involved in diverse cellular and physiological functions including cell-autonomous defense against pathogens [31–37]. Autophagy and its machinery can be utilized as one of the earliest eukaryotic defense mechanisms against viral pathogens [36]. In the context of bacterial invasion, TBK1 was found to be a crucial regulator of immunological autophagy. In response to bacterial products such as lipopolysaccharide (LPS), TLR4 activates TBK1 and NDP52 (an autophagic adaptor) recruits TBK1 into a complex with optineurin (OPTN, a key component of pathogen-induced autophagy), leading to the phosphorylation of OPTN and promoting the elimination of bacterial by OPTN-mediated xenophagy [32,38,39]. Furthermore, TBK1 also controls autophagic maturation [31]. Although both TBK1 and autophagy play crucial role in antiviral immunity, the roles of TBK1 in linking innate antiviral immunity with autophagy remains to be determined.

3. Negative regulation of TBK1

As a critical kinase involved in antiviral immunity, the activity of TBK1 must be tightly regulated to maintain immune homeostasis. TBK1 activity can be regulated in a variety of ways, such as phosphorylation, ubiquitination, kinase activity modulation and prevention of functional TBK1-containing complexes formation (Fig. 1).
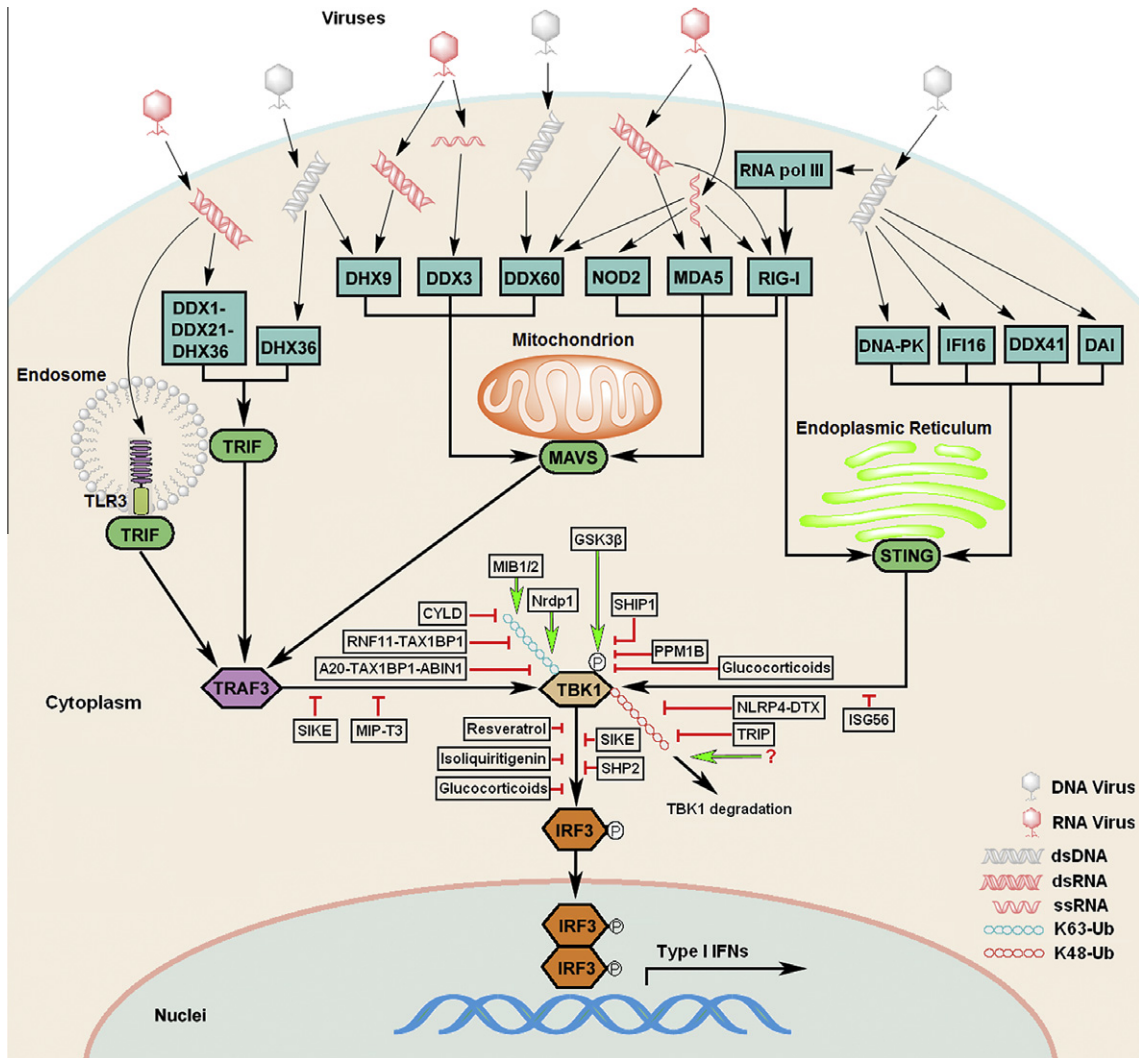
Fig. 1. Modulation of TBK1-mediated antiviral innate immunity. Following engagement by their cognate ligands, PRRs recruit different adaptor proteins (TRIF, MAVS or STING) to activate TBK1. Activated TBK1 then phosphorylates IRF3 and triggers its dimerization and nuclear translocation, leading to activation of type I IFN genes expression. TBK1 activity can be regulated by multiple molecules. GSK3β, SHIP1, PPM1B and glucocorticoids modulate TBK1 activity targeting its phosphorlation. MIB1/2, Nrdp1, CYLD, A20-TAX1BP1-ABIN1 complex and RNF11-TAX1BP1 complex modulate K63-linked ubiquitination of TBK1. TRIP and NLRP4-DTX complex suppress K48-linked ubiquitination of TBK1. SHP-2, resveratrol isoliquiritigenin and glucocorticoid inhibit TBK1 kinase activity. SIKE, MIP-T3 and ISG56 suppress TBK1-containing complex formation by competitive inhibition. Green arrow, stimulators; Red ground line, negative regulators.

3.1. Phosphorylation

Self-association and autophosphorylation at Ser172 of TBK1 is essential for its activation [40]. Recruiting of multiple TBK1 dimers to signaling complexes enables activation-loop swapping of locally clustered TBK1 and results in Ser172 phosphorylation [40,41]. Additional transautoactivation events occur due to high local concentration [40]. Furthermore, GSK3β binds with TBK1, facilitates TBK1 auto-phosphorylation at Ser172 within its kinase activation loop and promotes TBK1 activation upon viral infection [42]. Several phosphatases have been identified as regulators of phosphorylation of TBK1 to attenuated IFN-β production. For example, the inositol 5′ phosphatase SHIP-1, previously known as an important negative regulator of TLR4 signaling [43,44], targets TBK1 to inhibit TLR3-induced IFN-β production [45]. The absence of SHIP-1 resulted in constitutive association between TRAF3, TRIF, and TBK1, altered localization of the protein following TLR3 stimulation, and increased levels of phosphorylated TBK1 [45]. Protein phosphatase Mg^{2+}/Mn^{2+} dependent 1B (PPM1B; also called PP2Cβ) physiologically binds to TBK1 followed virus infection and dephosphorylates TBK1 at serine 172, leading to termination of TBK1-mediated IRF3 activation [46]. Furthermore, it has been reported that glucocorticoid hormones could inhibit TBK1 phosphorylation on Ser-172 [47].

3.2. Ubiquitination

In addition to phosphorylation/dephosphorylation, ubiquitination/deubiquitination is another essential posttranslational modification for the modulation of TBK1 activity. E3 ubiquitin ligase TRAF3 mediates lysine 63 (K63)-linked polyubiquitination of TBK1 and facilitates its activation [48]. E3 ubiquitin ligases mind bomb 1 and 2 (MIB1 and MIB2) [33] and Nrdp1 [49] activate TBK1 by promoting its K63-linked polyubiquitination. On the other hand, several deubiquitinases disrupt K63-linked polyubiquitination to terminate TBK1-mediated signaling transduction. For example, deubiquitinating enzyme cylindromatosis (CYLD) removes K63-linked polyubiquitin from TBK1 [50,51]. Harhaj and co-workers [52,53] identified A20 regulatory complex including ubiquitin-editing enzyme A20 (also known as TNFAIP3), Tax1-binding protein 1 (TAX1BP1, also known as T6BP or TXBP151) and A20 binding inhibitor of NF-κB 1 (ABIN1) antagonizes K63-linked polyubiquitination of TBK1. In this model, ABIN1 is recruited to ubiquitinated forms of TBK1/IKKε via its UBD and also recruits TAX1BP1 and A20 to form an A20 regulatory complex. The A20 complex disrupts interactions between TBK1/IKKε and TRAF3 to attenuate antiviral signaling. Recently, Charoenthongtrakul et al. reported that RING Finger Protein 11 (RNF11) cooperated with TAX1BP1 and attenuated K63-linked polyubiquitination of TBK1 to block IFN-β production [54].

K63-linked ubiquitination of TBK1 occurred early after viral infection, whereas K48-linked ubiquitination of TBK1 was observed at later times [38]. E3 ligases specifically target K48-linked ubiquitination of TBK1 could promote the degradation of TBK1 through proteasome and thus terminate downstream signaling transduction. NLR protein NLRP4 recruits the E3 ligase DTX4 to TBK1 for K48-linked polyubiquitination, which led to degradation of TBK1 [55]. Recently, we report that TRAF-interacting protein (TRIP), a virus-induced E3-ligase, negatively regulates antiviral response by promoting proteasomal degradation of TBK1 [56]. However, whether any deubiquitinating enzymes exist to specifically remove K48-linked ubiquitination of TBK1 and stabilizes its expression needs to be further investigated. The answer to this question may help to elucidate the complexities of modulation of TBK1 activity through ubiquitination/deubiquitination.

3.3. Kinase activity modulation

As a key kinase in antiviral immune responses, TBK1 directly mediates phosphorylation of IRF3 [8,9,57]. TBK1-mediated antiviral immunity could be regulated through modulation of its kinase activity. Interestingly, phosphatase Src homology 2 domain-containing protein tyrosine phosphatase 2 (SHP-2) could inhibit TBK1 activity through a phosphatase activity-independent mechanism [58]. C-terminal domain of SHP-2 directly binds with the kinase domain of TBK1 and thus inhibits its kinase activity and subsequent IFN-β production [58]. Several chemical compounds could suppress the kinase activity of TBK1, such as resveratrol (3′,4′,5′-trihydroxy-trans-stilbene, a polyphenol found in grapes and other plants) [59], isoliquiritigenin (ILG; a flavonoid with a chalcone structure) [60] and auranofin [an Au(I) compound with sulfur-linked organic ligands] [61]. Additionally, glucocorticoid dexamethasone could attenuate TBK1 activity through suppress its kinase activity, in addition to inhibiting its phosphorylation [47].

3.4. Prevention of functional TBK1-containing complexes formation

The formation of functional TBK1-containing complexes including TBK1, IKKε, TRAF3, IRF3 and other adaptors (TRIF, MAVS or Sting) is critical for TBK1 activity in antiviral immune responses. Thus, preventing the formation of functional TBK1-containing complexes is a major mechanism for negative regulation. For example, MIP-T3, which specifically interacts with TRAF3 but not other TRAF proteins, could impede the formation of functional TRAF3–TBK1 complexes to terminate IFN-β activation [62]. SIKE (Suppressor of IKKε) functions as a physiological suppressor of IKKε/TBK1 by sequesterin g IKKε/TBK1 in inactive complexes [63]. SIKE associated with TBK1 under physiological conditions and dissociated with TBK1 upon TLR3 engagement or viral infection. SIKE disrupts the interactions of IKKε or TBK1 with TRIF and IRF-3 and blocks the interaction of IKKε and TBK1 with RIG-I [63]. IFN-stimulated gene 56 (ISG56, also known as IFIT1) suppresses cellular antiviral responses through specific disruption of the MAVS–STING–TBK1 complex by steric hindrance [64].

OPTN, as a TBK1 binding partner, was reported to be involved in the regulation of TBK1 activity [65–67]. However, the effects of OPTN on TBK1 regulation are controversial. Mankouri et al. reported that OPTN was a negative regulator in the induction of IFN-β in response to RNA virus infection [66]. OPTN targets TBK1 to specific sites in the cell [66], and that this may prevent the TBK1-containing complexes formation. On the contrary, Gleason et al. demonstrated OPTN as an enhancer of TBK1 activity [67]. OPTN binds to polyubiquitylated species formed in response to LPS and poly(I:C), enhancing the activation of TBK1 that is required for optimal phosphorylation of IRF3 and production of IFN-β [67]. The discrepancy of OPTN in the regulation of TBK1 activity might be due to the fact that different cells used in these studies. Thus, the potential role and exact mechanism of OPTN in TBK1 activation require further investigation.

4. Viral evasion strategies targeting TBK1

Optimal activation of TBK1 and production of type I IFNs provide potent means of controlling viral infections. However, viruses have evolved elaborate strategies to disable the innate immune system [68]. It has been reported that several viruses could modulate TBK1 activity to circumvent IFN responses and facilitate viral replication, leading to the spread of viral infections (Fig. 2).

The leader proteinase (L^pro) of foot-and-mouth disease virus (FMDV) is a papain-like proteinase and plays an important role

in FMDV pathogenesis. Lb^{pro}, a shorter form of L^{pro}, has deubiquitinating activity and inhibited ubiquitination of TBK1 [69]. Papain-like protease domain 2 (PLP2), a catalytic domain of the non-structural protein 3 (nsp3) of mouse hepatitis virus A59 (MHV-A59) which is conserved for the Class II coronaviruses also mediates deubiquitination of TBK1 and inactivates its kinase activity to phosphorylate IRF3 [70]. In addition, PLP2 also delays the dissociation of IRF3 from TBK1, thereby effectively attenuates IFN induction [71]. The $\gamma_1$34.5 protein of herpes simplex viruses (HSV) and hepatitis C virus (HCV) NS3 protein could interact directly with TBK1, and that this binding disrupts the interaction of TBK1 and IRF3 [72–74]. NAP1 (NAK-associated protein 1), TANK and SINT-BAD (similar to NAP1 TBK1 adaptor) are three adaptor proteins that specifically bind TBK1/IKKε and participate in TLR/RLR-induced IFN production [75–77]. Modulation of these adaptor proteins could regulate IFN production [78]. Vaccinia virus (VACV) protein C6 is expressed early during infection and interacts with NAP1, TANK and SINTBAD [79]. Although C6 interact with all three scaffold proteins and inhibit IFN-β production, it does not affect their interaction with TBK1. Thus, the exact mechanism whereby C6 disrupts IRF3 activation remains not well determined [79]. K7, another VACV protein, also targets TBK1-containing protein complex [80]. Severe acute respiratory syndrome (SARS) coronavirus M protein and NY-1 hantavirus (NY1V) Gn cytoplasmic tail could suppress TRAF3–TBK1 complex formation [81–83]. The Tula virus (TULV), another hantavirus, regulates TBK1 activity through its Gn cytoplasmic tail [84]. However, the TULV Gn protein, unlike its pathogenic NY1V Gn cytoplasmic tail counterpart, is unable to bind TRAF3 [83,84]. The mechanism by which TULV and NY-1V Gn proteins regulate TBK1 complex remains to be further investigated. Borna disease virus (BDV) P protein physically associates with TBK1 and inhibits its kinase activity [85]. Open reading frame 45 (ORF45) of Kaposi's sarcoma-associated herpesvirus (KSHV) suppresses activation of IRF7 by competing with the associated IRF7 and inhibits its phosphorylation by TBK1 [86,87]. Poxvirus protein N1L [88] and HCV protease NS2 [89] could interact directly with TBK1 and reduce IRF3 activation and subsequent IFN-β expression. However, whether NIL and NS2 exert their inhibitory effects through steric hindrance of TBK-containing complex formation or suppression of TBK1 kinase activity remains unclear.

5. Small molecule inhibitors of TBK1

Several small molecule inhibitors specific for TBK1 have been discovered. These compounds can be used simply and rapidly and provide a complementary approach to the use of mouse knockouts or RNA interference technology. BX795 [originally developed as a 3-phosphoinositidedependent protein kinase 1 (PDK1)] [90] and a series of azabenzimidazole derivatives [91] inhibit both IKKε and TBK1 at low nanomolar concentrations [92]. But, these compounds lack selectivity as other kinases were also inhibited at low concentrations. Using a positional scanning peptide library (PSPL) technology, Hutti et al. [93] identified 227 compounds inhibit TBK1 activity at a concentration of 10 mM. However, none of these compounds were suitable inhibitors of TBK1 due to lacking specificity. Recently, McIver et al. developed a novel series of 2,4-diamino-5-cyclopropylpyrimidines as potent inhibitors of TBK1, with improved kinase selectivity. However, these compounds encountered unexpected toxicity at higher doses [94]. As TBK1 is a kinase of convergence for multiple pivotal signaling pathways, the further refinement of novel and specific TBK1 inhibitors may provide powerful new therapeutic drugs for many diseases, such as inflammatory disorders, autoimmune diseases and cancers. For example, the anticancer drug SU6668 (an indolinone compound), which was originally designed as a selective inhibitor of receptor tyrosine kinases involved in tumor vascularization [95], was further identified as a TBK1 inhibitor and modulated the proangiogenic role of the TBK1/IRF3 signaling axis in cancer development [96,97].

6. Conclusion

As summarized above, TBK1 is a critical integrator involved in the induction of type I IFNs in response to stimulation via PAMPs produced during replication of viruses. Besides its antiviral activity, TBK1 was also found to be involved in other signaling pathways, such as autophagy, apoptosis and oncogenesis. TBK1 controls autophagic maturation and plays crucial roles in antibacterial responses [31,32,98,99]. TBK1 was also involved in cellular transformation and oncogenesis [100–105]. Recently, Jin et al. reports that TBK1 controls IgA class switching by negatively regulating non-canonical NF-κB signaling [106]. Furthermore, the emerging role of TBK1 in a couple of diseases, including cancer and rheumatoid arthritis, was also elucidated [97,107,108]. Therefore, TBK1 will be potential promising targets for the development of therapeutic drugs for these diseases [97,109].

In the setting of antiviral immunity, multiple molecules were identified as TBK1 modulators and played crucial roles in maintaining immune homeostasis and effectively eliminating viral invasion. Furthermore, several compounds inhibitors specific for TBK1 were developed. As growing evidence implicates aberrant TBK1 activity in a variety of diseases, these identified regulators and small molecular compounds inhibitors of TBK1 provide strategies to modulate TBK1-mediated signaling pathway and may have therapeutic potential for the intervention of variety of diseases.
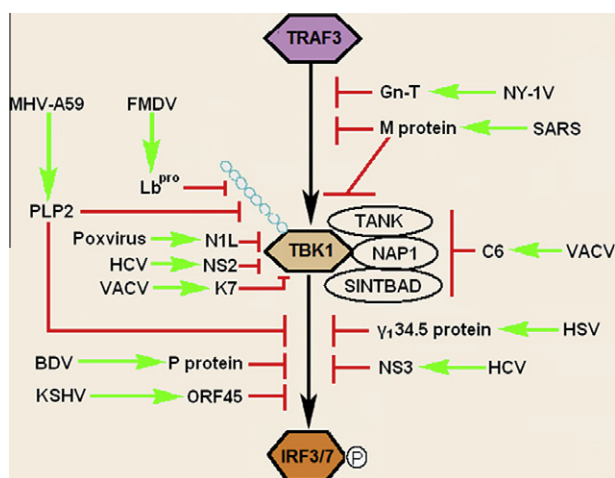
Fig. 2. Multiple viruses circumvent IFN responses by modulating TBK1 activity. A shorter form of leader proteinase (Lb^{pro}) of foot-and-mouth disease virus (FMDV) and papain-like protease domain 2 (PLP2) from mouse hepatitis virus A59 (MHV-A59) inhibit ubiquitination of TBK1. PLP2 also delays the dissociation of IRF3 from TBK1. The $\gamma_1$34.5 protein of herpes simplex viruses (HSV), hepatitis C virus (HCV) NS3 protein, vaccinia virus (VACV) protein C6 and K7, severe acute respiratory syndrome (SARS) coronavirus M protein and NY-1 hantavirus Gn cytoplasmic tail suppress TBK1-containing complex formation. Borna disease virus (BDV) P protein inhibits TBK1 kinase activity. Open reading frame 45 (ORF45) of Kaposi's sarcoma-associated herpesvirus (KSHV) inhibits phosphorylation of IRF7 by TBK1. Poxvirus protein N1L and HCV protease NS2 interact directly with TBK1 and inhibit its activity.

Acknowledgments

References

[1] Pomerantz, J.L. and Baltimore, D. (1999) NF-kappaB activation by a signaling complex containing TRAF2, TANK and TBK1, a novel IKK-related kinase. EMBO J. 18, 6694–6704.

[2] Tojima, Y., Fujimoto, A., Delhase, M., Chen, Y., Hatakeyama, S., Nakayama, K., Kaneko, Y., Nimura, Y., Motoyama, N., Ikeda, K., Karin, M. and Nakanishi, M. (2000) NAK is an IkappaB kinase-activating kinase. Nature 404, 778–782.

[3] Peters, R.T., Liao, S.M. and Maniatis, T. (2000) IKKepsilon is part of a novel PMA-inducible IkappaB kinase complex. Mol. Cell. 5, 513–522.

[4] Kishore, N., Huynh, Q.K., Mathialagan, S., Hall, T., Rouw, S., Creely, D., Lange, G., Caroll, J., Reitz, B., Donnelly, A., Boddupalli, H., Combs, R.G., Kretzmer, K. and Tripp, C.S. (2002) IKK-i and TBK-1 are enzymatically distinct from the homologous enzyme IKK-2: comparative analysis of recombinant human IKK-i, TBK-1, and IKK-2. J. Biol. Chem. 277, 13840–13847.

[5] Clark, K., Peggie, M., Plater, L., Sorcek, R.J., Young, E.R., Madwed, J.B., Hough, J., McIver, E.G. and Cohen, P. (2011) Novel cross-talk within the IKK family controls innate immunity. Biochem. J. 434, 93–104.

[6] McWhirter, S.M., Fitzgerald, K.A., Rosains, J., Rowe, D.C., Golenbock, D.T. and Maniatis, T. (2004) IFN-regulatory factor 3-dependent gene expression is defective in Tbk1-deficient mouse embryonic fibroblasts. Proc. Natl. Acad. Sci. USA 101, 233–238.

[7] Hemmi, H., Takeuchi, O., Sato, S., Yamamoto, M., Kaisho, T., Sanjo, H., Kawai, T., Hoshino, K., Takeda, K. and Akira, S. (2004) The roles of two IκB kinase-related kinases in lipopolysaccharide and double stranded RNA signaling and viral infection. J. Exp. Med. 199, 1641–1650.

[8] Fitzgerald, K.A., McWhirter, S.M., Faia, K.L., Rowe, D.C., Latz, E., Golenbock, D.T., Coyle, A.J., Liao, S.M. and Maniatis, T. (2003) IKKε and TBK1 are essential components of the IRF3 signaling pathway. Nat. Immunol. 4, 491–496.

[9] Sharma, S., tenOever, B.R., Grandvaux, N., Zhou, G.P., Lin, R. and Hiscott, J. (2003) Triggering the interferon antiviral response through an IKK-related pathway. Science 300, 1148–1151.

[10] Perry, A.K., Chow, E.K., Goodnough, J.B., Yeh, W.C. and Cheng, G. (2004) Differential requirement for TANK-binding kinase-1 in type I interferon responses to toll-like receptor activation and viral infection. J. Exp. Med. 199, 1651–1658.

[11] Yu, T., Yi, Y.S., Yang, Y., Oh, J., Jeong, D. and Cho, J.Y. (2012) The pivotal role of TBK1 in inflammatory responses mediated by macrophages. Mediators Inflamm. 2012, 979105.

[12] Stetson, D.B. and Medzhitov, R. (2006) Antiviral defense: interferons and beyond. J. Exp. Med. 203, 1837–1841.

[13] Theofilopoulos, A.N., Baccala, R., Beutler, B. and Kono, D.H. (2005) Type I interferons (alpha/beta) in immunity and autoimmunity. Annu. Rev. Immunol. 23, 307–336.

[14] Alexopoulou, L., Holt, A.C., Medzhitov, R. and Flavell, R.A. (2001) Recognition of double-stranded RNA and activation of NF-kappaB by Toll-like receptor 3. Nature 413, 732–738.

[15] Yoneyama, M., Kikuchi, M., Natsukawa, T., Shinobu, N., Imaizumi, T., Miyagishi, M., Taira, K., Akira, S. and Fujita, T. (2004) The RNA helicase RIG-I has an essential function in double-stranded RNA-induced innate antiviral responses. Nat. Immunol. 5, 730–737.

[16] Hornung, V., Ellegast, J., Kim, S., Brzózka, K., Jung, A., Kato, H., Poeck, H., Akira, S., Conzelmann, K.K., Schlee, M., Endres, S. and Hartmann, G. (2006) 5′-Triphosphate RNA is the ligand for RIG-I. Science 314, 994–997.

[17] Pichlmair, A., Schulz, O., Tan, C.P., Näslund, T.I., Liljeström, P., Weber, F. and Reis e Sousa, C. (2006) RIG-I-mediated antiviral responses to single-stranded RNA bearing 5′-phosphates. Science 314, 997–1001.

[18] Kato, H., Takeuchi, O., Sato, S., Yoneyama, M., Yamamoto, M., Matsui, K., Uematsu, S., Jung, A., Kawai, T., Ishii, K.J., Yamaguchi, O., Otsu, K., Tsujimura, T., Koh, C.S., Reis e Sousa, C., Matsuura, Y., Fujita, T. and Akira, S. (2006) Differential roles of MDA5 and RIG-I helicases in the recognition of RNA viruses. Nature 441, 101–105.

[19] Sabbah, A., Chang, T.H., Harnack, R., Frohlich, V., Tominaga, K., Dube, P.H., Xiang, Y. and Bose, S. (2009) Activation of innate immune antiviral responses by Nod2. Nat. Immunol. 10, 1073–1080.

[20] Ablasser, A., Bauernfeind, F., Hartmann, G., Latz, E., Fitzgerald, K.A. and Hornung, V. (2009) RIG-I-dependent sensing of poly(dA:dT) through the induction of an RNA polymerase III-transcribed RNA intermediate. Nat. Immunol. 10, 1065–1072.

[21] Chiu, Y.H., Macmillan, J.B. and Chen, Z.J. (2009) RNA polymerase III detects cytosolic DNA and induces type I interferons through the RIG-I pathway. Cell Signal. 138, 576–591.

[22] Takaoka, A., Wang, Z., Choi, M.K., Yanai, H., Negishi, H., Ban, T., Lu, Y., Miyagishi, M., Kodama, T., Honda, K., Ohba, Y. and Taniguchi, T. (2007) DAI (DLM-1/ZBP1) is a cytosolic DNA sensor and an activator of innate immune response. Nature 448, 501–505.

[23] Unterholzner, L., Keating, S.E., Baran, M., Horan, K.A., Jensen, S.B., Sharma, S., Sirois, C.M., Jin, T., Latz, E., Xiao, T.S., Fitzgerald, K.A., Paludan, S.R. and Bowie, A.G. (2010) IFI16 is an innate immune sensor for intracellular DNA. Nat. Immunol. 11, 997–1004.

[24] Kerur, N., Veettil, M.V., Sharma-Walia, N., Bottero, V., Sadagopan, S., Otageri, P. and Chandran, B. (2011) IFI16 acts as a nuclear pathogen sensor to induce the inflammasome in response to Kaposi Sarcoma-associated herpesvirus infection. Cell Host Microbe 9, 363–375.

[25] Ferguson, B.J., Mansur, D.S., Peters, N.E., Ren, H. and Smith, G.L. (2012) DNA-PK is a DNA sensor for IRF-3-dependent innate immunity. eLife 1, e00047.

[26] Zhang, Z., Yuan, B., Bao, M., Lu, N., Kim, T. and Liu, Y.J. (2011) The helicase DDX41 senses intracellular DNA mediated by the adaptor STING in dendritic cells. Nat. Immunol. 12, 959–965.

[27] Zhang, Z., Kim, T., Bao, M., Facchinetti, V., Jung, S.Y., Ghaffari, A.A., Qin, J., Cheng, G. and Liu, Y.J. (2011) DDX1, DDX21, and DHX36 helicases form a complex with the adaptor molecule TRIF to sense dsRNA in dendritic cells. Immunity 34, 866–978.

[28] Takeuchi, O. and Akira, S. (2009) Innate immunity to virus infection. Immunol. Rev. 227, 75–86.

[29] Platanias, L.C. (2005) Mechanisms of type-I- and type-II-interferon-mediated signalling. Nat. Rev. Immunol. 5, 375–386.

[30] Weidberg, H. and Elazar, Z. (2011) TBK1 mediates crosstalk between the innate immune response and autophagy. Sci. Signal. 4, pe39.

[31] Pilli, M., Arko-Mensah, J., Ponpuak, M., Roberts, E., Master, S., Mandell, M.A., Dupont, N., Ornatowski, W., Jiang, S., Bradfute, S.B., Bruun, J.A., Hansen, T.E., Johansen, T. and Deretic, V. (2012) TBK-1 promotes autophagy-mediated antimicrobial defense by controlling autophagosome maturation. Immunity 37, 223–234.

[32] Thurston, T.L., Ryzhakov, G., Bloor, S., von Muhlinen, N. and Randow, F. (2009) The TBK1 adaptor and autophagy receptor NDP52 restricts the proliferation of ubiquitin-coated bacteria. Nat. Immunol. 10, 1215–1221.

[33] Mizushima, N., Yoshimori, T. and Ohsumi, Y. (2011) The role of Atg proteins in autophagosome formation. Annu. Rev. Cell. Dev. Biol. 27, 107–132.

[34] Deretic, V. and Levine, B. (2009) Autophagy, immunity, and microbial adaptations. Cell Host Microbe 5, 527–549.

[35] Richetta, C. and Faure, M. (2012) Autophagy in antiviral innate immunity. Cell Microbiol., http://dx.doi.org/10.1111/cmi.12043 [Epub ahead of print].

[36] Yordy, B. and Iwasaki, A. (2011) Autophagy in the control and pathogenesis of viral infection. Curr. Opin. Virol. 1, 196–203.

[37] Kim, H.J., Lee, S. and Jung, J.U. (2010) When autophagy meets viruses: a double-edged sword with functions in defense and offense. Semin. Immunopathol. 32, 323–341.

[38] Galluzzi, L., Kepp, O. and Kroemer, G. (2011) Autophagy and innate immunity ally against bacterial invasion. EMBO J. 30, 3213–3214.

[39] Wild, P., Farhan, H., McEwan, D.G., Wagner, S., Rogov, V.V., Brady, N.R., Richter, B., Korac, J., Waidmann, O., Choudhary, C., Dotsch, V., Bumann, D. and Dikic, I. (2011) Phosphorylation of the autophagy receptor optineurin restricts Salmonella growth. Science 333, 228–233.

[40] Ma, X., Helgason, E., Phung, Q.T., Quan, C.L., Iyer, R.S., Lee, M.W., Bowman, K.K., Starovasnik, M.A. and Dueber, E.C. (2012) Molecular basis of Tank-binding kinase 1 activation by transautophosphorylation. Proc. Natl. Acad. Sci. USA 109, 9378–9383.

[41] Goncalves, A., Bürckstümmer, T., Dixit, E., Scheicher, R., Górna, M.W., Karayel, E., Sugar, C., Stukalov, A., Berg, T., Kralovics, R., Planyavsky, M., Bennett, K.L., Colinge, J. and Superti-Furga, G. (2011) Functional dissection of the TBK1 molecular network. PLoS One. 6, e23971.

[42] Lei, C.Q., Zhong, B., Zhang, Y., Zhang, J., Wang, S. and Shu, H.B. (2010) Glycogen synthase kinase 3β regulates IRF3 transcription factor-mediated antiviral response via activation of the kinase TBK1. Immunity 33, 878–889.

[43] Sly, L.M., Rauh, M.J., Kalesnikoff, J., Song, C.H. and Krystal, G. (2004) LPS induced upregulation of SHIP is essential for endotoxin tolerance. Immunity 21, 227–239.

[44] An, H., Xu, H., Zhang, M., Zhou, J., Feng, T., Qian, C., Qi, R. and Cao, X. (2005) Src homology 2 domain-containing inositol-5-phosphatase 1 (SHIP1) negatively regulates TLR4-mediated LPS response primarily through a phosphatase activity- and PI-3K-independent mechanism. Blood 105, 4685–4692.

[45] Gabhann, J.N., Higgs, R., Brennan, K., Thomas, W., Damen, J.E., Ben Larbi, N., Krystal, G. and Jefferies, C.A. (2010) Absence of SHIP-1 results in constitutive phosphorylation of tank-binding kinase 1 and enhanced TLR3-dependent IFN-beta production. J. Immunol. 184, 2314–2320.

[46] Zhao, Y., Liang, L., Fan, Y., Sun, S., An, L., Shi, Z., Cheng, J., Jia, W., Sun, W., Mori-Akiyama, Y., Zhang, H., Fu, S. and Yang, J. (2012) PPM1B negatively regulates antiviral response via dephosphorylating TBK1. Cell Signal. 24, 2197–2204.

[47] McCoy, C.E., Carpenter, S., Pålsson-McDermott, E.M., Gearing, L.J. and O'Neill, L.A. (2008) Glucocorticoids inhibit IRF3 phosphorylation in response to Toll-like receptor-3 and -4 by targeting TBK1 activation. J. Biol. Chem. 283, 14277–14285.

[48] Li, S., Wang, L., Berman, M., Kong, Y.Y. and Dorf, M.E. (2011) Mapping a dynamic innate immunity protein interaction network regulating type I interferon production. Immunity 35, 426–440.

[49] Wang, C., Chen, T., Zhang, J., Yang, M., Li, N., Xu, X. and Cao, X. (2009) The E3 ubiquitin ligase Nrdp1 'preferentially' promotes TLR-mediated production of type I interferon. Nat. Immunol. 10, 744–752.

[50] Friedman, C.S., O'Donnell, M.A., Legarda-Addison, D., Ng, A., Cárdenas, W.B., Yount, J.S., Moran, T.M., Basler, C.F., Komuro, A., Horvath, C.M., Xavier, R. and Ting, A.T. (2008) The tumour suppressor CYLD is a negative regulator of RIG-I-mediated antiviral response. EMBO Rep. 9, 930–936.

[51] Zhang, M., Wu, X., Lee, A.J., Jin, W., Chang, M., Wright, A., Imaizumi, T. and Sun, S.C. (2008) Regulation of IkappaB kinase-related kinases and antiviral responses by tumor suppressor CYLD. J. Biol. Chem. 283, 18621–18626.

[52] Parvatiyar, K., Barber, G.N. and Harhaj, E.W. (2010) TAX1BP1 and A20 inhibit antiviral signaling by targeting TBK1-IKKi kinases. J. Biol. Chem. 285, 14999–15009.

[53] Gao, L., Coope, H., Grant, S., Ma, A., Ley, S.C. and Harhaj, E.W. (2011) ABIN1 protein cooperates with TAX1BP1 and A20 proteins to inhibit antiviral signaling. J. Biol. Chem. 286, 36592–36602.

[54] Charoenthongtrakul, S., Gao, L., Parvatiyar, K., Lee, D. and Harhaj, E.W. (2013) RING Finger Protein 11 Targets TBK1/IKKi Kinases to Inhibit Antiviral Signaling. PLoS One. 8, e53717.

[55] Cui, J., Li, Y., Zhu, L., Liu, D., Songyang, Z., Wang, H. and Wang, R. (2012) NLRP4 negatively regulates type I interferon signaling by targeting the kinase TBK1 for degradation via the ubiquitin ligase DTX4. Nat. Immunol. 13, 387–395.

[56] Zhang, M., Wang, L., Zhao, X., Zhao, K., Meng, H., Zhao, W. and Gao, C. (2012) TRAF-interacting protein (TRIP) negatively regulates IFN-β production and antiviral response by promoting proteasomal degradation of TANK-binding kinase 1. J. Exp. Med. 209, 1703–1711.

[57] Mori, M., Yoneyama, M., Ito, T., Takahashi, K., Inagaki, F. and Fujita, T. (2004) Identification of Ser-386 of interferon regulatory factor 3 as critical target for inducible phosphorylation that determines activation. J. Biol. Chem. 279, 9698–9702.

[58] An, H., Zhao, W., Hou, J., Zhang, Y., Xie, Y., Zheng, Y., Xu, H., Qian, C., Zhou, J., Yu, Y., Liu, S., Feng, G. and Cao, X. (2006) SHP-2 phosphatase negatively regulates the TRIF adaptor protein-dependent type I interferon and proinflammatory cytokine production. Immunity 25, 919–928.

[59] Youn, H.S., Lee, J.Y., Fitzgerald, K.A., Young, H.A., Akira, S. and Hwang, D.H. (2005) Specific inhibition of MyD88-independent signaling pathways of TLR3 and TLR4 by resveratrol: molecular targets are TBK1 and RIP1 in TRIF complex. J. Immunol. 175, 3339–3346.

[60] Park, S.J. and Youn, H.S. (2010) Isoliquiritigenin suppresses the Toll-interleukin-1 receptor domain-containing adapter inducing interferon-beta (TRIF)-dependent signaling pathway of Toll-like receptors by targeting TBK1. J. Agric. Food. Chem. 58, 4701–4705.

[61] Park, S.J., Lee, A.N. and Youn, H.S. (2010) TBK1-targeted suppression of TRIF-dependent signaling pathway of toll-like receptor 3 by auranofin. Arch. Pharm. Res. 33, 939–945.

[62] Ng, M.H., Ho, T.H., Kok, K.H., Siu, K.L., Li, J. and Jin, D.Y. (2011) MIP-T3 is a negative regulator of innate type I IFN response. J. Immunol. 187, 6473–6482.

[63] Huang, J., Liu, T., Xu, L.G., Chen, D., Zhai, Z. and Shu, H.B. (2005) SIKE is an IKK epsilon/TBK1-associated suppressor of TLR3- and virus-triggered IRF-3 activation pathways. EMBO J. 24, 4018–4028.

[64] Li, Y., Li, C., Xue, P., Zhong, B., Mao, A.P., Ran, Y., Chen, H., Wang, Y.Y., Yang, F. and Shu, H.B. (2009) ISG56 is a negative-feedback regulator of virus-triggered signaling and cellular antiviral response. Proc. Natl. Acad. Sci. USA 106, 7945–7950.

[65] Morton, S., Hesson, L., Peggie, M. and Cohen, P. (2008) Enhanced binding of TBK1 by an optineurin mutant that causes a familial form of primary open angle glaucoma. FEBS Lett. 582, 997–1002.

[66] Mankouri, J., Fragkoudis, R., Richards, K.H., Wetherill, L.F., Harris, M., Kohl, A., Elliott, R.M. and Macdonald, A. (2010) Optineurin negatively regulates the induction of IFNbeta in response to RNA virus infection. PLoS Pathog. 6, e1000778.

[67] Gleason, C.E., Ordureau, A., Gourlay, R., Arthur, J.S. and Cohen, P. (2011) Polyubiquitin binding to optineurin is required for optimal activation of TANK-binding kinase 1 and production of interferon β. J. Biol. Chem. 286, 35663–35674.

[68] Taylor, K.E. and Mossman, K.L. (2012) Recent advances in understanding viral evasion of type I interferon. Immunology, http://dx.doi.org/10.1111/imm.12038 [Epub ahead of print].

[69] Wang, D., Fang, L., Li, P., Sun, L., Fan, J., Zhang, Q., Luo, R., Liu, X., Li, K., Chen, H., Chen, Z. and Xiao, S. (2011) The leader proteinase of foot-and-mouth disease virus negatively regulates the type I interferon pathway by acting as a viral deubiquitinase. J. Virol. 85, 3758–3766.

[70] Zheng, D., Chen, G., Guo, B., Cheng, G. and Tang, H. (2008) PLP2, a potent deubiquitinase from murine hepatitis virus, strongly inhibits cellular type I interferon production. Cell Res. 18, 1105–1113.

[71] Wang, G., Chen, G., Zheng, D., Cheng, G. and Tang, H. (2011) PLP2 of mouse hepatitis virus A59 (MHV-A59) targets TBK1 to negatively regulate cellular type I interferon signaling pathway. PLoS One 6, e17192.

[72] Otsuka, M., Kato, N., Moriyama, M., Taniguchi, H., Wang, Y., Dharel, N., Kawabe, T. and Omata, M. (2005) Interaction between the HCV NS3 protein and the host TBK1 protein leads to inhibition of cellular antiviral responses. Hepatology 41, 1004–1012.

[73] Verpooten, D., Ma, Y., Hou, S., Yan, Z. and He, B. (2009) Control of TANK-binding kinase 1-mediated signaling by the gamma(1)34.5 protein of herpes simplex virus 1. J. Biol. Chem. 284, 1097–1105.

[74] Ma, Y., Jin, H., Valyi-Nagy, T., Cao, Y., Yan, Z. and He, B. (2012) Inhibition of TANK binding kinase 1 by herpes simplex virus 1 facilitates productive infection. J. Virol. 86, 2188–2196.

[75] Sasai, M., Shingai, M., Funami, K., Yoneyama, M., Fujita, T., Matsumoto, M. and Seya, T. (2006) NAK-associated protein 1 participates in both the TLR3 and the cytoplasmic pathways in type I IFN induction. J. Immunol. 177, 8676–8683.

[76] Guo, B. and Cheng, G. (2007) Modulation of the interferon antiviral response by the TBK1/IKKi adaptor protein TANK. J. Biol. Chem. 282, 11817–11826.

[77] Ryzhakov, G. and Randow, F. (2007) SINTBAD, a novel component of innate antiviral immunity, shares a TBK1-binding domain with NAP1 and TANK. EMBO J. 26, 3180–3190.

[78] Zhao, W., Wang, L., Zhang, M., Wang, P., Yuan, C., Qi, J., Meng, H. and Gao, C. (2012) Tripartite motif-containing protein 38 negatively regulates TLR3/4-

and RIG-I-mediated IFN-β production and antiviral response by targeting NAP1. J. Immunol. 188, 5311–5318.

[79] Unterholzner, L., Sumner, R.P., Baran, M., Ren, H., Mansur, D.S., Bourke, N.M., Randow, F., Smith, G.L. and Bowie, A.G. (2011) Vaccinia virus protein C6 is a virulence factor that binds TBK-1 adaptor proteins and inhibits activation of IRF3 and IRF7. PLoS Pathog. 7, e1002247.

[80] Schröder, M., Baran, M. and Bowie, A.G. (2008) Viral targeting of DEAD box protein 3 reveals its role in TBK1/IKKepsilon-mediated IRF activation. EMBO J. 27, 2147–2157.

[81] Siu, K.L., Kok, K.H., Ng, M.H., Poon, V.K., Yuen, K.Y., Zheng, B.J. and Jin, D.Y. (2009) Severe acute respiratory syndrome coronavirus M protein inhibits type I interferon production by impeding the formation of TRAF3.TANK.TBK1/IKKepsilon complex. J. Biol. Chem. 284, 16202–16209.

[82] Alff, P.J., Gavrilovskaya, I.N., Gorbunova, E., Endriss, K., Chong, Y., Geimonen, E., Sen, N., Reich, N.C. and Mackow, E.R. (2006) The pathogenic NY-1 hantavirus G1 cytoplasmic tail inhibits RIG-I- and TBK-1-directed interferon responses. J. Virol. 80, 9676–9686.

[83] Alff, P.J., Sen, N., Gorbunova, E., Gavrilovskaya, I.N. and Mackow, E.R. (2008) The NY-1 hantavirus Gn cytoplasmic tail coprecipitates TRAF3 and inhibits cellular interferon responses by disrupting TBK1-TRAF3 complex formation. J. Virol. 82, 9115–9122.

[84] Matthys, V., Gorbunova, E.E., Gavrilovskaya, I.N., Pepini, T. and Mackow, E.R. (2011) The C-terminal 42 residues of the Tula virus Gn protein regulate interferon induction. J. Virol. 85, 4752–4760.

[85] Unterstab, G., Ludwig, S., Anton, A., Planz, O., Dauber, B., Krappmann, D., Heins, G., Ehrhardt, C. and Wolff, T. (2005) Viral targeting of the interferon-{beta}-inducing Traf family member-associated NF-{kappa}B activator (TANK)-binding kinase-1. Proc. Natl. Acad. Sci. USA 102, 13640–13645.

[86] Zhu, F.X., King, S.M., Smith, E.J., Levy, D.E. and Yuan, Y. (2002) A Kaposi's sarcoma-associated herpesviral protein inhibits virus-mediated induction of type I interferon by blocking IRF-7 phosphorylation and nuclear accumulation. Proc. Natl. Acad. Sci. USA 99, 5573–5578.

[87] Liang, Q., Fu, B., Wu, F., Li, X., Yuan, Y. and Zhu, F. (2012) ORF45 of Kaposi's sarcoma-associated herpesvirus inhibits phosphorylation of interferon regulatory factor 7 by IKKε and TBK1 as an alternative substrate. J. Virol. 86, 10162–10172.

[88] DiPerna, G., Stack, J., Bowie, A.G., Boyd, A., Kotwal, G., Zhang, Z., Arvikar, S., Latz, E., Fitzgerald, K.A. and Marshall, W.L. (2004) Poxvirus protein N1L targets the I-kappaB kinase complex, inhibits signaling to NF-kappaB by the tumor necrosis factor superfamily of receptors, and inhibits NF-kappaB and IRF3 signaling by toll-like receptors. J. Biol. Chem. 279, 36570–36578.

[89] Kaukinen, P., Sillanpää, M., Nousiainen, L., Melén, K. and Julkunen, I. (2013) Hepatitis C virus NS2 protease inhibits host cell antiviral response by inhibiting IKKε and TBK1 functions. J. Med. Virol. 85, 71–82.

[90] Feldman, R.I., Wu, J.M., Polokoff, M.A., Kochanny, M.J., Dinter, H., Zhu, D., Biroc, S.L., Alicke, B., Bryant, J., Yuan, S., Buckman, B.O., Lentz, D., Ferrer, M., Whitlow, M., Adler, M., Finster, S., Chang, Z. and Arnaiz, D.O. (2005) Novel small molecule inhibitors of 3-phosphoinositide-dependent kinase-1. J. Biol. Chem. 280, 19867–19874.

[91] Wang, T., Block, M.A., Cowen, S., Davies, A.M., Devereaux, E., Gingipalli, L., Johannes, J., Larsen, N.A., Su, Q., Tucker, J.A., Whitston, D., Wu, J., Zhang, H.J., Zinda, M. and Chuaqui, C. (2012) Discovery of azabenzimidazole derivatives as potent, selective inhibitors of TBK1/IKKepsilon kinases. Bioorg. Med. Chem. Lett. 22, 2063–2069.

[92] Clark, K., Plater, L., Peggie, M. and Cohen, P. (2009) Use of the pharmacological inhibitor BX795 to study the regulation and physiological roles of TBK1 and IkappaB kinase epsilon: a distinct upstream kinase mediates Ser-172 phosphorylation and activation. J. Biol. Chem. 284, 14136–14146.

[93] Hutti, J.E., Porter, M.A., Cheely, A.W., Cantley, L.C., Wang, X., Kireev, D., Baldwin, A.S. and Janzen, W.P. (2012) Development of a high-throughput assay for identifying inhibitors of TBK1 and IKKε. PLoS One 7, e41494.

[94] McIver, E.G., Bryans, J., Birchall, K., Chugh, J., Drake, T., Lewis, S.J., Osborne, J., Smiljanic-Hurley, E., Tsang, W., Kamal, A., Levy, A., Newman, M., Taylor, D., Arthur, J.S., Clark, K. and Cohen, P. (2012) Synthesis and structure-activity relationships of a novel series of pyrimidines as potent inhibitors of TBK1/IKKε kinases. Bioorg. Med. Chem. Lett. 22, 7169–7173.

[95] Laird, A.D., Vajkoczy, P., Shawver, L.K., Thurnher, A., Liang, C., Mohammadi, M., Schlessinger, J., Ullrich, A., Hubbard, S.R., Blake, R.A., Fong, T.A., Strawn, L.M., Sun, L., Tang, C., Hawtin, R., Tang, F., Shenoy, N., Hirth, K.P., McMahon, G. and Cherrington. (2000) SU6668 is a potent antiangiogenic and antitumor agent that induces regression of established tumors. Cancer Res. 60, 4152–4162.

[96] Godl, K., Gruss, O.J., Eickhoff, J., Wissing, J., Blencke, S., Weber, M., Degen, H., Brehmer, D., Orfi, L., Horváth, Z., Kéri, G., Müller, S., Cotton, M., Ullrich, A. and Daub, H. (2005) Proteomic characterization of the angiogenesis inhibitor SU6668 reveals multiple impacts on cellular kinase signaling. Cancer Res. 65, 6919–6926.

[97] Lee, D.F. and Hung, M.C. (2008) Advances in targeting IKK and IKK-related kinases for cancer therapy. Clin. Cancer. Res. 14, 5656–5662.

[98] Watson, R.O., Manzanillo, P.S. and Cox, J.S. (2012) Extracellular M. tuberculosis DNA targets bacteria for autophagy by activating the host DNA-sensing pathway. Cell Signal. 150, 803–815.

[99] Radtke, A.L., Delbridge, L.M., Balachandran, S., Barber, G.N. and O'Riordan, M.X. (2007) TBK1 protects vacuolar integrity during intracellular bacterial infection. PLoS Pathog. 3, e29.

[100] Bonnard, M., Mirtsos, C., Suzuki, S., Graham, K., Huang, J., Ng, M., Itié, A., Wakeham, A., Shahinian, A., Henzel, W.J., Elia, A.J., Shillinglaw, W., Mak, T.W., Cao, Z. and Yeh, W.C. (2000) Deficiency of T2K leads to apoptotic liver degeneration and impaired NF-kappaB-dependent gene transcription. EMBO J. 19, 4976–4985.

[101] Chien, Y., Kim, S., Bumeister, R., Loo, Y.M., Kwon, S.W., Johnson, C.L., Balakireva, M.G., Romeo, Y., Kopelovich, L., Gale Jr., M., Yeaman, C., Camonis, J.H., Zhao, Y. and White, M.A. (2006) RalB GTPase-mediated activation of the IkappaB family kinase TBK1 couples innate immune signaling to tumor cell survival. Cell Signal. 127, 157–170.

[102] Delhase, M., Kim, S.Y., Lee, H., Naiki-Ito, A., Chen, Y., Ahn, E.R., Murata, K., Kim, S.J., Lautsch, N., Kobayashi, K.S., Shirai, T., Karin, M. and Nakanishi, M. (2012) TANK-binding kinase 1 (TBK1) controls cell survival through PAI-2/serpinB2 and transglutaminase 2. Proc. Natl. Acad. Sci. USA 109, E177–186.

[103] Clément, J.F., Meloche, S. and Servant, M.J. (2008) The IKK-related kinases: from innate immunity to oncogenesis. Cell Res. 18, 889–899.

[104] Ou, Y.H., Torres, M., Ram, R., Formstecher, E., Roland, C., Cheng, T., Brekken, R., Wurz, R., Tasker, A., Polverino, T., Tan, S.L. and White, M.A. (2011) TBK1 directly engages Akt/PKB survival signaling to support oncogenic transformation. Mol. Cell. 41, 458–470.

[105] Korherr, C., Gille, H., Schäfer, R., Koenig-Hoffmann, K., Dixelius, J., Egland, K.A., Pastan, I. and Brinkmann, U. (2006) Identification of proangiogenic genes and pathways by high-throughput functional genomics: TBK1 and the IRF3 pathway. Proc. Natl. Acad. Sci. USA 103, 4240–4245.

[106] Jin, J., Xiao, Y., Chang, J., Yu, J., Hu, H., Starr, R., Brittain, G.C., Chang, M., Cheng, X. and Sun, S. (2012) The kinase TBK1 controls IgA class switching by negatively regulating noncanonical NF-κB signaling. Nat. Immunol. 13, 1101–1109.

[107] Shen, R.R. and Hahn, W.C. (2011) Emerging roles for the non-canonical IKKs in cancer. Oncogene 30, 631–641.

[108] Hammaker, D., Boyle, D.L. and Firestein, G.S. (2012) Synoviocyte innate immune responses: TANK-binding kinase-1 as a potential therapeutic target in rheumatoid arthritis. Rheumatology 51, 610–618.

[109] Niederberger, E., Möser, C., Kynast, K. and Geisslinger, G. (2012) The non-canonical IκB kinases IKKε and TBK1 as potential targets for the development of novel therapeutic drugs. Curr. Mol. Med. [Epub ahead of print].