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 IκKε (another IKK-related kinase) and the canonical IKKs, IκKα and IκKβ [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 IκKα: phosphorylate IκKα/β, decreasing the activity of the canonical IKK complex [5]. On the other hand, IκKα/β phosphorylate and directly activate TBK1 and IκKε [5].

TBK1 could induce IκB degradation and NF-κB activity through IκKβ [1,2]. However, studies with TBK1 and IκKα: 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 IκKα to phosphorylate transcript factors IRF3 and IRF7, leading to the induction of type I IFN (IFN-α/β) [6–10]. Although TBK1 and IκKα have indistinguishable activities in inducing type I IFN expression and subsequent antiviral responses, they do not seem to be redundant and exhibit differential expression patterns and substrates specificity [8,11]. TBK1 is ubiquitously expressed, whereas IκKα 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) [15–17], DNA-dependent activator of IFN-regulatory factors (DAI; also known as IFI16) [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], IFN-γ-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],...
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 (IF-NAR) 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).
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 transautophosphorylation 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’ phosphate 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]. Harhay 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-kB 1 (ABIN1) antagonizes K63-linked polyubiquitination of TBK1. In this model, ABIN1 targets TBK1 to inhibit its kinase activity, in addition to inhibiting its phosphorylation [47].

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 auranoj (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 sequestering 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 IFT1) 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 protease (L(pro)) of foot-and-mouth disease virus (FMDV) is a papain-like proteinase and plays an important role
in FMDV pathogenesis. Lbpro, a shorter form of Lpro, 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 γ34.5 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 SINTBAD (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 Gc cytoplasmic tail [84]. However, the TULV Gc protein, unlike its pathogenic NY1V Gn cytoplasmic tail counterpart, is unable to bind TRAF3 [83,84]. The mechanism by which TULV and NY-1V Gc 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 TBK1-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-phosphoinositide-depotendent protein kinase 1 (PKD1)] [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, Hutt 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 indololn 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.

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