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Review

Recent insights into the complexity of Tank-binding kinase 1 signaling networks: The emerging role of cellular localization in the activation and substrate specificity of TBK1

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ABSTRACT

Tank-binding kinase 1 (TBK1) serves as an important component of multiple signaling pathways. While the majority of research on TBK1 has focused on its role in innate immunity, critical functions for TBK1 in autophagy and cancer are beginning to emerge. This review highlights recent structural and biochemical studies that provide insights into the molecular mechanism of TBK1 activation and summarizes what is known to date about TBK1 substrate selection. Growing evidence suggests that both processes rely on TBK1 subcellular localization, with a variety of adaptor proteins each directing TBK1 to discrete signaling complexes for different cellular responses. Further study of TBK1-mediated pathways will require careful consideration of TBK1 mechanisms of activation and specificity for proper dissection of these distinct signaling cascades.

Introduction to TBK1 function and molecular architecture

Living cells use complex signaling networks to monitor and respond to their environment. This cellular circuitry relies on specialized "node" proteins that can receive upstream inputs and modulate do

These protei
ubiquitin lig
tors), which when activated by inputs, use their catalytic activity to output signal to downstream substrates. In addition to their catalytic subunits, node proteins often contain discrete protein–protein interaction domains or motifs that mediate associations with other members of the pathway and/or regulate their signaling behavior [2,3]. Thus, these accessory domains can act as gating elements for node proteins much in the same way components like transistors help control current flow (output) in response to an applied voltage (input) in electronic circuitry. Indeed, the presence of multiple interaction domains can lead to complex switch behavior for these proteins that can be critical for proper signal transduction and cellular response [4–6].

TBK1 functions as a key node protein in several cell signaling pathways, including innate immune response [7,8], xenophagic elimination of bacteria [9–13] and, under pathological conditions, cell growth and proliferation [8,14–18]. TBK1 is composed of a kinase domain (KD) that houses its catalytic activity and three acces-

[19,20]. Recent structural studies of TBK1 and the related kinase, IKKβ, reveal a common domain architecture for these kinases [21,22]. Together, the KD, ULD and DD form a joint, three-way interface that, in the context of obligate dimerization, positions the kinase active sites facing away from one another (Fig. 1). This configuration strongly disfavors productive kinase–kinase contact within the dimer, thereby limiting TBK1 autophosphorylation and activation in the absence of upstream signaling.

TBK1 activation is primarily controlled by localization

Upon pathway stimulation, TBK1 is recruited to signaling complexes via its AB motif [23,24]. Here local clustering of TBK1 molecules can allow interdimer KD interactions that lead to trans-autophosphorylation. As observed in the crystal structure of a TBK1 fragment comprising the KD and ULD, neighboring TBK1

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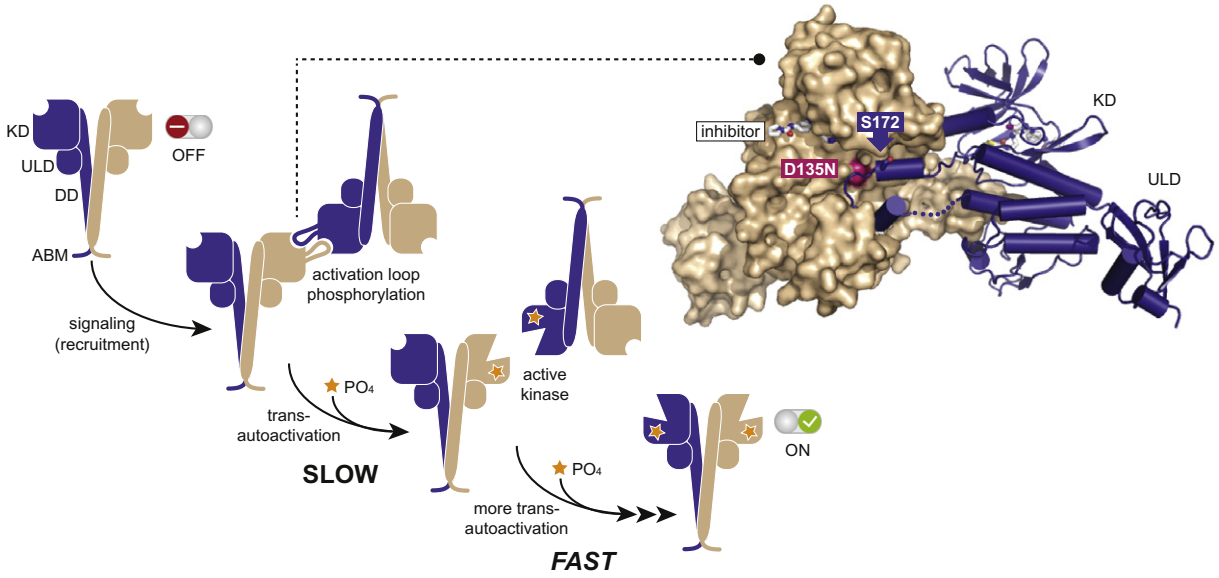

Fig. 1. Proposed mechanism of TBK1 trans-autophosphorylation. TBK1 forms stable homodimers, with each protomer (one colored blue and one colored tan) consisting of a KD, ULD, DD and AB motif. The tripartite KD-ULD-DD interface within each TBK1 protomer fixes the kinase active sites facing away from one another in the context of the dimer (TBK1 "OFF"). Binding of the AB motif to adaptor molecules (e.g. TANK, SINTBAD, NAP1) recruits TBK1 to distinct signaling complexes when upstream pathways are stimulated. This results in high local concentrations of TBK1, which facilitates interdimer interactions that enable autophosphorylation and activation of the KD. Specifically, activation loop swapping—observed between neighboring KDs within the asymmetric unit of a crystal lattice—provides important structural elements required for an active kinase conformation (i.e. docking of the "EF" helix onto the C-terminal lobe of the adjacent KD). These interactions also place the activation residue, Ser172, in close proximity to the catalytic Asp135 residue (D135N; dark pink) of the neighboring KD. Once activated, pSer172-TBK1 can then rapidly phosphorylate the remaining TBK1 pool, to form fully activated kinase dimers (TBK1 "ON"). Figure adapted from Ma et al. 2012.

molecules can interact via an activation loop-swapped conformation (Fig. 1) [21]. These interactions serve to both supply critical structural elements/contacts required to achieve an active kinase conformation, as well as place the activation segment within the catalytic cleft of the adjacent KD for phosphotransfer to the activation residue, Ser172. Similar activation segment swapping has also been observed in structures from other kinase families, where transient kinase–kinase interactions facilitate trans-autophosphorylation events [25–27]. Yet, unlike these other kinases (e.g. DAP3K, SLK, LOK and CHK2), which appear to phosphorylate their non-consensus site activation loop sequences only in the context of the loop-swapped conformation, activated TBK1 also readily phosphorylates its activation loop sequence as a classical substrate [21]. Therefore, while kinetic analyses suggest that the initial loop-swapped phosphorylation mechanism is relatively slow, once activated TBK1 is produced, it can rapidly activate the remaining pool of unphosphorylated TBK1 [21].

Given the robust autophosphorylation capabilities of the TBK1 KD, important regulatory mechanisms are in place to ensure that TBK1 does not improperly fire in the absence of pathway stimulation. As highlighted above, localization plays a key role in the activation of this node protein; TBK1 is inactive until adaptor proteins recruit it to signaling complexes where it can be autophosphorylated due to high local concentration [28], or phosphorylated by other kinases [29] localized to the same molecular scaffold. In terms of electronic circuitry, TBK1 is thus analogous to a toggle switch. When expressed at endogenous levels, TBK1 requires the AB motif and upstream signaling for recruitment and activation. However, TBK1 overexpression can override this localization-based regulation, leading to activation in the absence of a competent AB motif or pathway stimulus [23].

Additionally, the ULD and DD also serve to autoinhibit the KD. As illustrated in Fig. 1, the structure of the TBK1 dimer effectively "ties" the KD back-to-back with itself, thereby limiting autophosphorylation [21,22]. Indeed, autoinhibition of catalytic domains by accessory domains/motifs is actually a common gating behavior observed for node proteins. Often the regulatory elements will sterically block the enzyme active site (e.g. SH2-containing phosphatase 2 and Twitchin kinase) [30,31], or make intramolecular interactions that lock the enzyme in an inactive conformation (e.g. Src and c-Abl kinases) [32–34]. Although the TBK1 ULD and DD do not physically occlude the kinase active site or allosterically control the catalytic competency of the KD, these accessory domains do act to autoinhibit TBK1 by restricting self-associations that lead to autophosphorylation of the TBK1 activation loop. Consistent with this model of conformational control, TBK1 constructs lacking the DD were shown to accumulate substantially higher levels of Ser172 phosphorylation during expression and purification than full-length TBK1 dimer despite the fact that these dimerization-defective variants were expressed at much lower levels and, moreover, were co-expressed with a phosphatase to limit pSer172 modification [21]. Thus, conformational regulation provides an additional layer of control to TBK1 activation.

TBK1 substrate specificity is also likely driven by localization

Once Ser172 is phosphorylated, the TBK1 activation loop folds back onto the C-terminal lobe of the KD to complete the apparent binding site for polypeptide substrates [21]. The composition of this site (depicted by electrostatic surface representation in Fig. 2a) suggests that TBK1 would favor a hydrophobic residue at the P + 1 position (where P0 is the site of modification). Indeed, the TBK1 activation loop sequence, which is rapidly phosphorylated by activated TBK1, contains a leucine at this location [21]. Comparison of 80 published TBK1 substrate sequences (Fig. 2b and Supplementary Table S1) finds that hydrophobic residues comprise the P + 1 position in ~70% of the substrates; however, residues such as serine, proline, glutamine and aspartate are also tolerated at this site. Aside from this seeming preference for hydrophobic sidechains at P + 1, there is little sequence conservation surrounding the phospho-site of TBK1 substrates. Previously reported consensus motifs flanking the P0 serine/threonine residue (Fig. 2b)

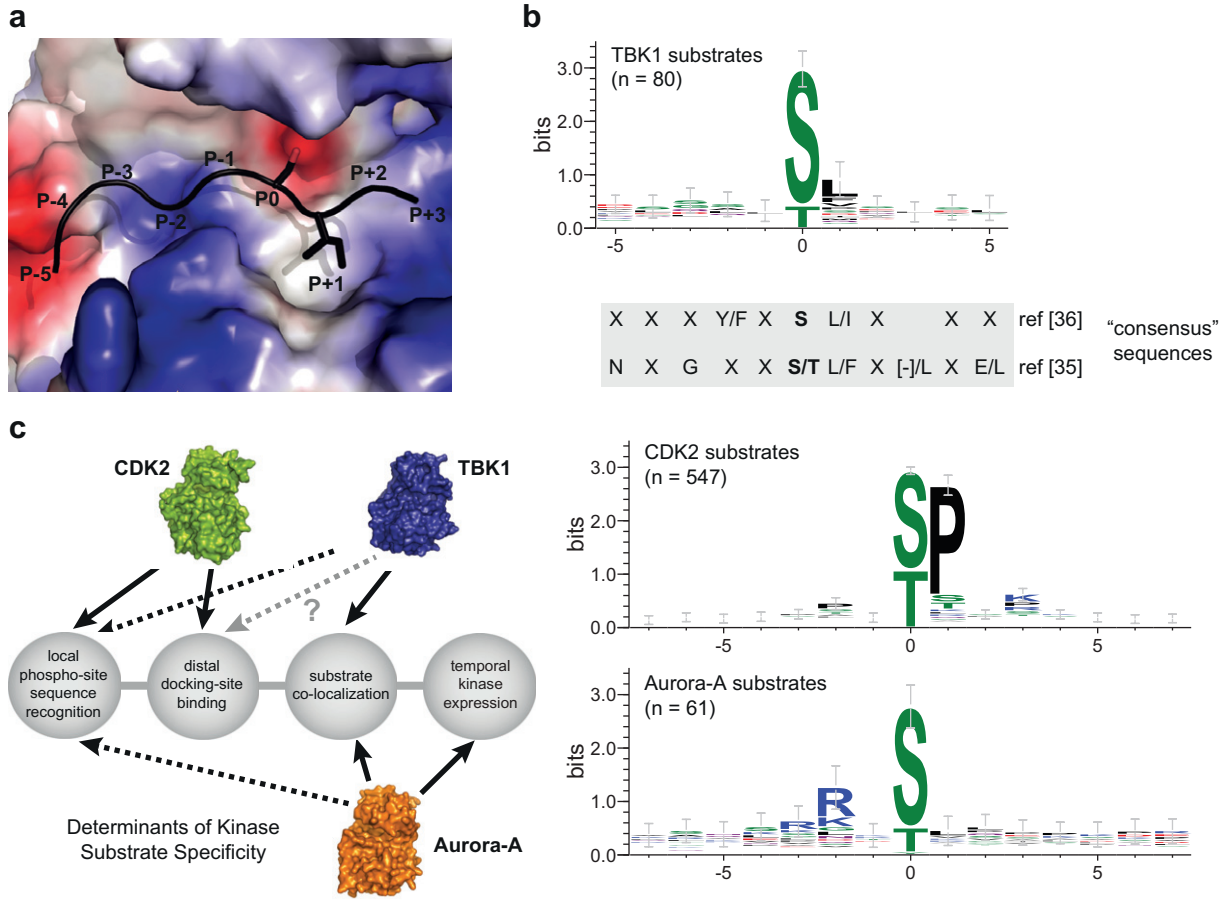

Fig. 2. Kinases and substrate specificity. (A) Electrostatic surface representation of the TBK1 KD catalytic cleft bound to a modeled peptide substrate (PDB IDs 4EUU and 1ATP, respectively). The active kinase structure suggests that TBK1 would prefer a hydrophobic residue in the P + 1 position of the substrate (shown as an ILE residue). (B) A logo plot of TBK1 substrate sequences ($n = 80$) reveals minimal conservation of local phospho-site sequences. Published TBK1 phospho-site "consensus" sequences derived from narrower native substrate alignments or phosphorylation studies using peptide libraries are listed below for comparison. (C) Kinases use a variety of mechanisms to achieve substrate specificity, ranging from local phospho-site sequence recognition to temporal expression level. Two cell-cycle kinases, CDK2 and Aurora-A, show varying dependency on local consensus-site identity (right, logo plots) and utilize different combinations of specificity determinants to achieve substrate selection. TBK1 appears to use localization to guide substrate specificity. All sequence logos generated using WebLogo 3.3.

[35,36] appear to fall off when comparing a large panel of natural TBK1 substrates.

These findings imply that TBK1 substrate selectivity does not depend greatly on local phospho-site sequences of downstream targets. In fact, kinase specificity can be determined by a number of other molecular mechanisms, including distal docking-site binding of substrates, co-localization with substrates and temporal regulation of kinase expression level (as reviewed in Bhattacharyya et al. 2006 [3] and Ubersax and Ferrell 2007 [37]). Fig. 2c illustrates how these different kinase specificity determinants can be combined to establish substrate selectivity for two distinct cell-cycle kinases, cyclin-dependent kinase 2 (CDK2) and Aurora-A kinase, in comparison to TBK1.

Sequence alignments of CDK2 substrates (Supplementary Table S2) show that, unlike TBK1, CDK2 has a strong, local-sequence specificity surrounding its substrate phospho-sites. CDK2 vastly prefers proline in the P + 1 position while it favors, albeit to a lesser degree, basic residues in the P + 3 position (Fig. 2c, top logo plot) [38,39]. Moreover, the formation of CDK2-cyclin complexes helps guide target selection by extending substrate recognition sites onto the adjacent surface of the bound cyclin subunit [40–45]. To date, these kinds of distal docking-site interactions have not been observed for TBK1-substrate pairs. Although the related kinase IKKβ utilizes its ULD and DD subunits to restrict phospho-site selection on its substrate, IκBα [22], enzymatic analysis of purified TBK1 constructs reveals that removal of these accessory domains does not seem to alter the specificity of TBK1 for sites on two disparate macromolecular substrates [21]. TBK1 substrate specificity therefore appears to be maintained wholly within the KD; yet, it is possible that additional substrate-docking sites exist on the TBK1 KD apart from binding at the catalytic cleft. Many kinases contain secondary docking sites on their catalytic domain—the functional equivalents of "exosites" in proteases—that interact with conserved substrate motifs for proper target recognition. While such interactions have not been identified for TBK1 and its diverse array of substrates (see Table 1), it is formally possible that they exist. In a similar vein, it is also conceivable that TBK1 complexes may help direct substrate selection akin to the CDK2-cyclin complex described above. Continued research on TBK1-substrate interactions will hopefully clarify whether either of these mechanisms is relevant in TBK1 target selection.

Still, these are not the only specificity determinants used by kinases. Temporal regulation of substrate or kinase expression levels can also help define kinase specificity [37]. In the case of CDK2, the kinase concentration remains fairly constant, but variations in cyclin levels throughout the cell cycle serve to drive CDK2 specificity for different targets [46–48]. By contrast, Aurora-A kinase expression levels are directly modulated by transcriptional upregulation in G2 and M phases [49], where its activity controls spindle assembly and stability, and then reduced

Table 1
TBK1 substrates.[a] (See above-mentioned references for further information.)

Substrate	Protein function	Phosphorylation site(s)	Detection method[b]	References
Act1	E3 ubiquitin ligase	S162, S220, S233	in vitro [γ-^{32}P]ATP, S→A mutations	[98]
cRel	transcription factor	S479, S602	in vitro [γ-^{32}P]ATP peptides	[99]
mDDX3X	helicase	S181, S183, S240, S269, S429, T438, S442, S456, S520, T542, S543	in vitro [γ-^{32}P]ATP peptide array	[35]
IκBα	inhbitor of NFκB	S36	in vitro [γ-^{32}P]ATP, S36A	[100]
IKKα	kinase	unknown	in vitro [γ-^{32}P]ATP	[29]
IKKβ	kinase	unknown	in vitro [γ-^{32}P]ATP	[29]
		S177, S181	in vitro [γ-^{32}P]ATP, S177A+S181A	[100]
IRF3	transcription factor	S173, S175	in vitro, MS	[101]; Fig S1
		S339	in vivo +/-(TBK1&IKKε) shRNA, WB	[102]
		S385, T404, S405	in vitro, MS	[103]; Fig S1
		S386	in vitro MS; in vitro WB	[21,101, 103]
		T390	in vitro MS	[101]; Fig S1
		S396	in vitro MS; in vitro WB	[21,101,103 ,104]
		S398	in vitro MS	[21,103]
		S402	in vitro MS	[103,104]; Fig S1
IRF7	transcription factor	S471, S472	in vitro [γ-^{32}P]ATP, S471A+S472A	[105]
		S477, S479	in vitro [γ-^{32}P]ATP, S477A+S479A or S479A	[106]
NEMO	adaptor	T50, S141, S148, S196, S208	co-transfection MS	[91]
mNIK	kinase	S48, S89, S113, S153, S349, S354, S357, T690, S728, S752, S820, S821	co-transfection MS	[107]
		S862	co-transfection MS, S862A	[107]
p65/RelA	transcription factor	S536	in vitro [γ-^{32}P]ATP, S536A	[108]
PELI1	E3 ubiquitin ligase	S76, T288, S293	in vitro MS	[109]
		T80	in vitro, tryptic HPLC, total MS, sequencing	[109]
		T86	in vitro, MS	[109]
STAT6	transcription factor	S407	in vitro [γ-^{32}P]ATP, S407A	[80]
STING	receptor/adaptor	S324, S326	co-transfection gel shift, S324A+S326A	[110]
		S358	co-transfection, gel shift, S358A (MS)	[110]
TANK	adaptor	S49, S126, S178, S208, S228, S257	co-transfection, MS	[29]
TBK1	kinase	S172	in vitro peptide array; in vivo S172A or K38A; in vitro MS	[21,35]
TRIM27	E3 ubiquitin ligase	unknown	co-transfection, IP; in vitro [γ-^{32}P]ATP	[111]
XIAP	E3 ubiquitin ligase	S430	in vitro MS, S430A	[112]
mLRRK2	kinase	S910, S935 S995	in vitro WB, in vivo +/- inhibitor, MS in vivo +/- inhibitor, MS	[113]
OPTN	autophagy receptor	S177	in vitro gel shift, S→A mutations, co-transfection +/- inhibitor or phosphatase, MS	[11]
p62	autophagy receptor	S403	in vitro [γ-^{32}P]ATP, S403A	[13]
Akt	kinase	T195, T308, S378, S473	in vitro MS or WB	[15,18,21, 95]
Sec5	exocyst component	unknown	in vitro [γ-^{32}P]ATP	[14]
IR	receptor kinase	S994	in vitro [γ-^{32}P]ATP peptide, S994A	[114]

[a] Substrates that contain experimentally verified TBK1 phospho-sites are listed and grouped by general output pathway: immune response/inflammation, autophagy, proliferation/growth and insulin signaling. All substrates are human proteins except for murine DDX3X (mDDX3X), NIK (mNIK) and LRRK2 (mLRRK2) proteins. Act1, NF-κB activator 1; cRel, proto-oncogene; IκBα, inhibitory κBα protein; IKKα, inhibitor of κB kinase alpha; IKKβ, inhibitor of κB kinase beta; IRF3, interferon regulatory factor 3; IRF7, interferon regulatory factor 7; NEMO, NFκB essential modulator; mNIK, murine NFκB-inducing kinase; p65/RelA, NFκB p65/RelA subunit; PELI1, Pellino-1; STAT6, signal transducer and activator of transcription 6; STING, stimulator of IFN genes; TANK, TRAF-associated NF-κB activator; TBK1, Tank-binding kinase 1; TRIM27, Tripartite motif-containing protein 27; XIAP, X-linked inhibitor of apoptosis protein; mLRRK2, murine leucine-rich repeat kinase 2; OPTN, Optineurin; p62, Sequestosome-1; Akt, Akt-1; Sec5, Exocyst complex component 2; IR, insulin receptor.

[b] Detection methods are listed according to the particular phospho-site, with the corresponding reference(s) in the adjacent column. MS denotes mass spec; WB denotes Western blot; IP denotes immunoprecipitation.

via proteasomal degradation later in mitosis [50–52]. Aurora-A also shows a moderate preference for basic residues in the P−2 and P−3 positions (Fig. 2c, bottom log plot and Supplementary Table S3) [53]; however, much of its specificity is derived from its recruitment to the mitotic spindle via interactions with the microtubule-binding protein, TPX2 [54–56].

Although TBK1 levels do not appear to fluctuate like Aurora-A [7], there is compelling evidence that TBK1 may use localization

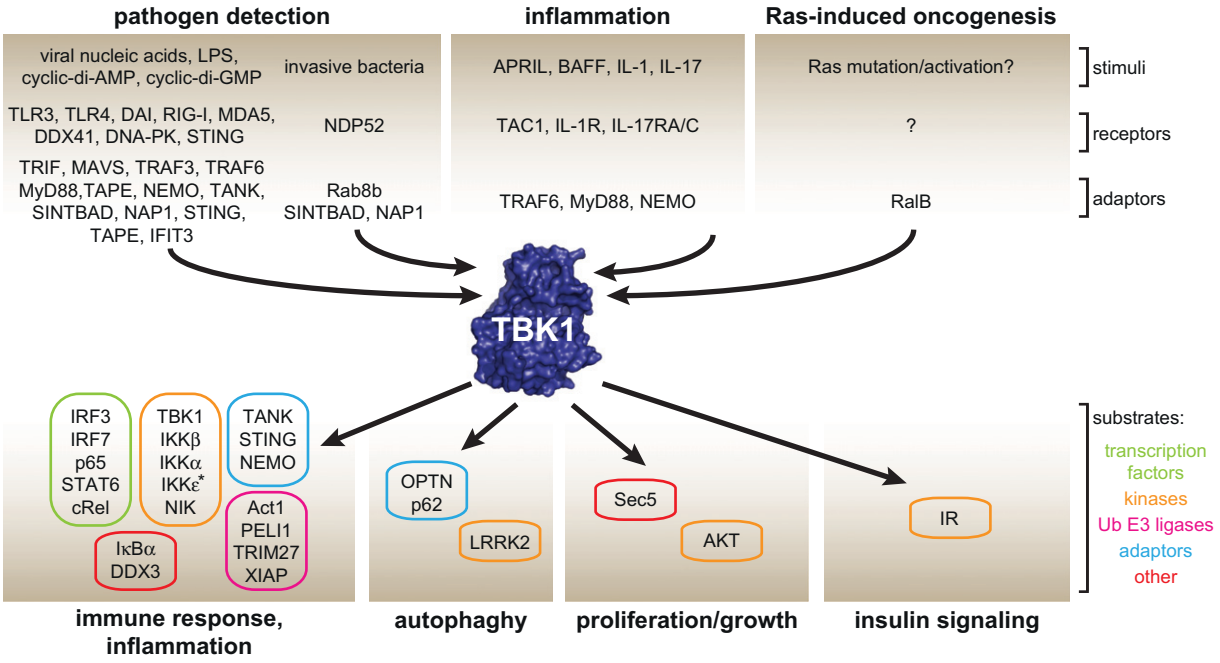

Fig. 3. TBK1 is an important node protein for multiple signaling pathways. TBK1 integrates a variety of upstream signals and directly modulates the function of numerous downstream targets. Adaptor proteins appear to play a critical role in determining how TBK1 is recruited to distinct signaling complexes, activated and directed towards specific substrates. IKKε is denoted with any asterisk because, to our knowledge, no direct evidence of IKKε phosphorylation by TBK1 has been published to date—IKKε is presumed to be a TBK1 substrate based on homology with TBK1.

as a key specificity determinant. Proteomic studies have demonstrated that TBK1 forms separate complexes with adaptor proteins such as TANK, SINTBAD and NAP1—interactions that lead to different subcellular localization of TBK1 [7,23,57]. Immunofluorescence microscopy reveals diffuse perinuclear staining for TANK while SINTBAD and NAP1 are characterized by discrete foci. Interestingly, co-expression of TBK1 with NAP1 changes the cellular distribution of TBK1 from diffusely cytosolic to punctate, with foci that largely co-localize with NAP1 [23]. These adaptors compete for binding to the C-terminal AB motif of TBK1 to form mutually exclusive complexes with the kinase. Because the adaptors in turn have unique binding partners, they serve to recruit TBK1 to distinct signaling complexes, thereby directing TBK1 activity towards specific downstream pathways (Fig. 3) [7]. For example, TANK–TBK1 interactions appear to be required for proper IFN-β production in response to viral infection or poly(I:C) stimulation [23] whereas SINTBAD and NAP1 are important for TBK1-mediated elimination of cytosolic bacterial pathogens via selective autophagy [9].

The discovery of new TBK1 adaptors such as TBK1-associated protein in endolysosomes (TAPE) [58] and IFN-induced protein with tetratricopeptide repeats 3 (IFIT3), which bridges TBK1 to the mitochondrial anti-viral signaling (MAVS) protein [59], further support the concept of subcellular localization as part of TBK1 signaling. Moreover, TBK1 ubiquitination and binding to NEMO [60] can be likened to the scaffolding/localization-driven substrate specificity NEMO dictates for IKKβ, as shown by Schröfelbauer et al. [61]. Indeed, in light of the critical role of K63-linked ubiquitin in TBK1-mediated pathways [62–72], one can imagine how ubiquitin chains might provide a platform for the assembly of TBK1 signaling complexes given that many TBK1 adaptors and substrates bind ubiquitin (e.g. NEMO, SINTBAD, NAP1, NDP52, and OPTN) [9,11,60]. These findings, taken together with the lack of a strong phospho-site consensus sequence or apparent secondary docking sites for TBK1, implies that TBK1 localization is crucial, not only for its activation, but for its substrate specificity, as well. Recent evidence for the assembly of large, stimulus-specific, TBK1 signaling platforms (functional protein aggregates and clusters on membrane compartments) supports this model of localized TBK1 activation and signal propagation [28,69,73].

Certainly, this mode of target selection is by no means a novel concept in the kinase field. Co-localization or "co-recruitment" of kinases and substrates is increasingly cited as a means of driving kinase specificity [74]. Recent work has even shown that recruitment strategies can override catalytic domain-substrate interactions in determining kinase targets [75]. Finally, it is important to note that the adaptor-mediated recruitment of TBK1 to distinct signaling complexes/pathways described above does not necessarily rely on exact scaffolding geometries of TBK1 and substrates for proper signal transduction. Engineered localization strategies and mathematical modeling suggest that simply increasing the encounter frequency between a kinase and substrate by raising their local concentrations is sufficient to propagate signal [76–78]. Such a mechanism would allow TBK1 to readily accommodate the wide array of disparate substrates that it phosphorylates; a growing list that includes other kinases, transcription factors, ubiquitin (Ub) E3 ligases and adaptor proteins (see Table 1).

The complexity of TBK1 signaling pathways and implications for unraveling TBK1-related pathologies

Perhaps more striking than the sheer number or functional variety of TBK1 substrates is the diversity of the broader signaling networks that utilize TBK1 as a node protein, which include immune response, inflammation, autophagy, cell proliferation and growth and insulin signaling (Fig. 3). To date, the majority of TBK1 research has focused on the role of the kinase in innate immune pathways that lead to type 1 interferon response, such as Toll-like receptor (e.g. TLR3 and TLR4) and cytosolic viral DNA/RNA receptor (e.g. RIG-I and MDA5) signaling [58,59,67,69,71,73,79–92]. As mentioned above, studies have also defined a role for TBK1 in the degradation of invasive bacteria, via ubiquitin-mediated clearance mechanisms [9–12]. While this latter pathway also falls under

the umbrella of cellular response to pathogen detection, it ultimately engages autophagy machinery to eliminate cytosolic bacteria (xenophagy) as opposed to inducing transcriptional upregulation of interferons and inflammation to combat infection. Intriguingly, TBK1 has very recently been implicated as an upstream regulator in the autophagic clearance of protein aggregates associated with glaucoma [93] and various neurodegenerative diseases [94], as well as a critical component of the elevated basal autophagy observed in *KRAS*-dependent non-small cell lung cancer (NSCLC) [17]. These studies suggest that a better understanding of TBK1's role in autophagy may prove important in elucidating the molecular mechanisms of TBK1-related pathologies—a key step for evaluating and potentially exploiting TBK1 as a therapeutic target.

Indeed, much remains unknown as to how TBK1 is activated and what substrates are targeted under pathological conditions; however, as in normal TBK1 signaling, there does appear to be some degree of pathway selection involved. For example, although TBK1 activity is essential for certain *KRAS*-driven cancers, there is no evidence of IRF3 activation in these cancer cell lines [16]. Thus, TBK1 is not globally activated against all potential substrates in these cells, but instead appears to be directed towards specific downstream targets in this disease state. What these targets are, and how TBK1 finds them is not fully understood. Similarly, while TBK1 has been shown to activate the oncogenic AKT kinase, it is unclear what upstream signals would precipitate this interaction [15,18,95]. Given the potential for TBK1 auto-activation upon over-expression and the fact that transient transfection stimulates TBK1-mediated innate immune pathways, common experimental approaches may prove inadequate in properly dissecting these distinct signaling cascades. To this end, recent advances in TBK1 inhibitor specificity provide improved tools to address these experimental concerns [29,36,96,97]. If careful attention is paid to how future studies are conducted and analyzed, continued research on these emerging pathways will hopefully yield key insights into TBK1 biology and establish important inroads into treating TBK1-related diseases.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.febslet.2013.01.059.

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