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REVIEW

TAK1 mediates convergence of cellular signals for death and survival

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Abstract
TGF-β activated kinase 1, a MAPK kinase kinase family serine threonine kinase has been implicated in regulating diverse range of cellular processes that include embryonic development, differentiation, autophagy, apoptosis and cell survival. TAK1 along with its binding partners TAB1, TAB2 and TAB3 displays a complex pattern of regulation that includes serious crosstalk with major signaling pathways including the C-Jun N-terminal kinase (JNK), p38 MAPK, and I-kappa B kinase complex (IKK) involved in establishing cellular commitments for death and survival. This review also highlights how TAK1 orchestrates regulation of energy homeostasis via AMPK and its emerging role in influencing mTORC1 pathway to regulate death or survival in tandem.

Keywords Apoptosis · Autophagy · Cytokine · Inflammatory · Smad

TAK1, a multifunctional kinase

Transforming growth factor-β is a versatile cytokine, regulating a wide variety of intracellular signaling pathways. The Smad dependent signaling pathway is conventionally acknowledged as the traditional pathway promoted by TGF-β1 [1]. However, the Smad dependent signaling pathway does not unfold the myriad functions of TGF-β1. Accumulating evidence suggests that the TGF-β1 multifunctionality is associated with the activation of diverse Smad independent pathways that may or may not involve crosstalk with Smads [2, 3]. TGF-β1, TGF-β2, and TGF-β3 are the three mammalian isoforms of TGF-β of which TGF-β1 represents the predominant isoform and the epitome of the TGF-β superfamily. TGF-β1 regulates a wide array of cellular functions including cell growth, differentiation, wound healing and apoptosis. TGF-β1 is also a puissant inducer in ECM synthesis [4, 5].

TGF-β1 signals originate with the interaction of type I and type II TGF-β receptors to activate distinct intracellular pathways [6]. Apart from the canonical Smad dependent pathways, the non-canonical, Smad independent pathways are directly activated by ligand-occupied receptors to regulate a wide array of downstream cellular responses [2, 7, 8]. Various branches of MAP kinase pathways including the extracellular signal regulated kinase (Erk) ½ [3, 9], p38 MAPK [10, 11], c-Jun N-Terminal kinase (JNK) [12, 13], phosphatidylinositol-3-kinase/AKT pathway [14, 15] and Rho-like GTPase [16, 17] signaling pathways are included among the Smad independent pathways. TGF-β-activated kinase 1 (TAK1) has emerged as an indispensable signaling molecule in Smad-independent TGF-β-induced signaling pathways. TAK1 is also a prime upstream molecule in TGF-β1 induced expression of fibronectin and type I collagen via activation of MKK4-JNK and MKK3-p38 signaling pathways respectively [18–20].

TAK1, a serine/threonine kinase, was first discovered as a member of the MAPK kinase kinase (MAP3K) family, named as MAP3K7, and is activated by TGF-β1 [21]. TAK1 is an extensively expressed kinase, which, as the name implies, was originally spotted as a TGFβ-activated enzyme [22, 23]. In addition to TGF-β1, TAK1 can be activated by various other stimuli encompassing lipopolysaccharides [24], pro-inflammatory cytokines like interleukin (IL)-1 [25], tumor necrosis factor (TNF)-α [26] and environmental stress [27]. TAK1 was originally recognized as a kinase in the TGF-β pathway by complementation and rescue of MAPKK mutant of yeast. TAK1 has been identified by a cDNA library screening and protein-fragment complementation assay in yeast for its tendency to substitute for the MAPKKK Ste11p in the yeast pheromone-induced MAPK

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pathway. Thereby, TAK1 was substantiated as a member of the MAPKKK family (MAP3K7) [22]. It is the only member of MAP3K family that has been found to be directly involved in TGF-β1 signaling. TAK1 activates TGF-β signaling and inturn gets activated by it [22]. After activation, TAK1 in turn, activates crucial intra-cellular kinases; the C-Jun N-terminal kinase (JNK), p38 MAPK, and I-kappa B kinase complex (IKK) [25, 28]. TAK1 is implicated in regulating the non-canonical Wnt signaling and hence functions as a negative feedback control of canonical wnt signaling [29]. Evidences indicate that TAK1 can promote the expression of Smad7 to regulate TGF-β induced Smad signaling [30]. TAK1 also interacts with the MH2 domain of Smads thereby impeding the transactivation of R-Smads [31]. Apart from regulating the functions of Smads, a crosstalk exists among the Smads and the downstream effectors of TAK1 such as ATF2 and p38MAPK to regulate the expression of TGF-β1 target genes [10, 32, 33]. These results conjointly indicate that TAK1 might be the converging point among different signaling pathways triggered by various signals. TAK1 is implicated in regulating differentiation, cell survival and inflammatory responses. TAK1 is involved in regulating apoptosis. It may stimulate or impede apoptosis depending upon the type of cells and tissues [34, 35]. TAK1 has also been found to be involved in activating pVHL [36] and LKB1 [37], which are the eminent tumor suppressor proteins.

TAK1 binding proteins

Among the MAP3K family members, TAK1 is peculiar in that its activation requires the assembly with specific binding partner proteins known as TAK1 binding protein 1, TAK1 binding protein 2, and TAK1 binding protein 3 (TAB1, TAB2, and TAB3) [38–40]. TAB1 interacts constitutively with TAK1 mediating the autophosphorylation of TAK1 [23]. TAB1 and TAB2 are structurally disparate TAK1 binding proteins, whereas TAB3 is related to TAB2 and shares 48% amino acid sequence with TAB2. TAB2 and TAB3 are suggested to function redundantly in mediating TAK1 activation. These proteins are thought to bind at specific regions of TAK1. The TAB1 binding region and the kinase domain of TAK1 span through the N-terminus of TAK1, while the TAB2/3 binding region lies within the C-terminus of TAK1 [39, 40]. TAB1 mediates autophosphorylation of TAK1 at two threonine residues (Thr-184 and Thr-187) and a serine residue (Ser-192) in the kinase activation loop. These phosphorylations are indispensable for TAK1 kinase activity [23, 38, 41–43]. Considerable body of evidence has implicated cell type specificity in the requirement of specific TAK1 binding partners. The TNF-α induced activation of TAK1 involves a signaling complex with TAB1 and TAB2 in Hela cells [44]. TAB3, a TAB2 related protein is involved in IL-1 and TNF-α signaling pathways [39, 40]. The demand for TAK1 binding partners also appears to be stimuli dependent. Studies in TAB1 null mouse embryonic fibroblasts have revealed that the activation of TAK1 by osmotic stress is TAB1 dependent. However, the activation of TAK1 by IL-1 and TNF-α is independent of TAB1 [45]. In glomerular messengial cells, TAB1 is necessary for TAK1 activation induced by TGF-β1 [41]. In vivo studies have also manifested that TAK1-TAB1 complex is vital for morphogenesis and the normal development of embryo. The global inactivation of TAB1 terminates in embryonic lethality and also leads to defects in development of vital organs like lungs and heart [46]. TAK1 deletion results in early embryonic lethality because of its role in myriad signaling pathways. $TAB1^{-/-}$ mice have abnormalities in cardiovascular and lung development and die during late stages of gestation. $TAB2^{-/-}$ mice have dysregulations in liver development and are embryonically lethal [28, 46, 47]. These findings indicate that TAB1 and TAB2 are not functionally redundant and have discrete roles in regulating TAK1 activity.

TAB1 and TAB2 isolated by the yeast two-hybrid screening using TAK1 protein as bait co-precipitated with endogenous TAK1 in many types of cells. TAB2 and its homolog TAB3 are found to bind ubiquitin to function as an adaptor, tethering TAK1 to the IKK complex [48, 49]. In contrast, the role of TAB1 in TAK1 signaling under the physiological setting has not yet been explored. In culture cells, TAB1 is found to be constitutively associated with TAK1 [43]. TAK1 when expressed alone does not show any kinase activity, however, its co-expression with TAB1 makes it kinetically active [23, 43]. Ectopic expression of TAB1 together with TAK1 induces TAK1 autophosphorylation and thereby activates TAK1 kinase activity in vitro [43]. The 68 amino acid residues present at the C-terminus of TAB1 are essential for binding to TAK1 and induction of autophosphorylation/activation [42]. The amino acid residues 480–495, located at the carboxy terminus of TAB1, play an indispensable role in its binding to TAK1 [42]. It has been seen that truncation of this region to just 24 amino acid residues (480–504) renders TAK1 completely autophosphorylated but only partially active [38]. Mutational analysis further contemplates Phe484 to be vital in this association. In vitro studies suggest that 67 residues (437–504) of TAB1 are enough for full activation of TAK1 [42]. The regulation of the activity of TAK1 by its N-terminal region is not quite clear. However, the deletion of 21 N-terminal amino acid residues in TAK1 (TAK1-ΔN) renders it constitutively active and TAB-1 independent in TGF-β signaling in MC3T3-E1 and MV1Lu cells [22, 23]. The activity of TAK1-ΔN is completely dependent on TAB-1 in Hela cells to argue for cell type specificity of the role of TGF-β in TAK1 activation [38]. N-terminal 77 amino acid fragment of TAK1 has been shown to inhibit activation

of TAK1, suggesting an autoinhibitory role of this domain in TAK1 activation [50]. A fusion protein consisting of the 303 residues at the amino terminus of TAK1 (Met1–Gln303) fused via a linker of five residues to the carboxy terminal 67 residues of TAB1 (Gln437–Pro504) shows higher levels of kinase activity when expressed in HeLa cells. This activity was not further increased following co-expression with TAB1, suggesting that only a minimal region of TAB1 is required for TAK1 activation [51]. The association between the C-terminal region of TAB1 and the catalytic domain of TAK1 stimulates activation of TAK1. This association may lead to a change in conformation of the kinase domain of TAK1, increasing the kinase activity of TAK1 to autophosphorylate at Thr-184, Thr-187 and Ser-192 in its activation loop. The autophosphorylated TAK1 then phosphorylates TAB1 at the C-terminal Ser/Thr rich region. Phosphorylated TAB1 still remains associated with TAK1, to possibly have the negatively charged phosphate groups of TAB1 influence the conformation of TAK1 further [38, 42, 43] .

TAB2 and its homolog, TAB3, act as adapters in TAK1 signaling. TAK1 constitutively interacts with TAB-1 without any influence on TAK1 activity [43, 52]. Upon stimulation with IL-1, both TAK1 and TAB-1 are recruited to TRAF6, thus triggering the activation of TAK1. Recent studies have shown that TAB2 is the adapter protein that serves to link TAK1 and TRAF-6. However, in absence of IL-1 stimulation an endogenous negative regulator may inactivate TAK1–TAB1 complex [52]. The domain structure of TAB2 consists of three conserved regions: a CUE domain, involved in ubiquitin binding [48], a coiled-coil domain, mediating interaction of TAB2 with TAK1 [52], and a zinc finger domain involved in poly-ubiquitin binding [52]. Previous reports have shown that TAK1 also contains coiled-coil α- helices at its C-terminus, which mediate its interaction with TAB2 [23]. This coiled coil domain may function as the site of interaction between TAK1 and TAB2. TAB2 and TAB3 bind both to TAK1 and the polyubiquitin chain, thereby bringing the polyubiquitinated proteins TRAF6, RIP1 and the IKK complex in close vicinity of TAK1 [49, 53, 54]. Research based evidences have shown that TAB2 is not vital for IL-1 signaling because of the compensatory role played by TAB3 [28, 47]. However, single knockout of TAB2 in mice leads to embryonic lethality at embryonic day 13.5 [47], suggesting that TAB2 has some peculiar functions that cannot be counter balanced by TAB3. Both the TAK1/TAB2 and the TAK1/TAB3 complex activate IKK in ubiquitin dependent fashion. However, mutating a conserved cysteine residue in the zinc finger domain (cysteine 706) to alanine or deleting the entire zinc finger domain of TAB3 quashes its potential to activate IKK. Also the deletion of CUE domain of TAB3 reduces its ability to activate IKK suggesting that the CUE domain may facilitate the activation of IKK and NF-κB but the zinc finger domain is the mandatory signaling domain for IKK and NF-κB activation [49] (Fig. 1).

Crystal structure of TAK1

The crystal structure of TAK1–TAB1 consists of a fold typical of protein kinases [55, 56]. The crystal structure of co-precipitated complex of un-phosphorylated TAK1–TAB1 (Ile31–Gln304:His468–Pro504) with adenosines has been determined. It consists of a large C-terminal lobe (residues 111–303) and a small N-terminal lobe (residues 31–104) connected through a flexible hinge region. This hinge region lies in a cleft between the N and the C terminal lobes of the complex. The hinge region forms a part of the catalytically active site of the complex wherein adenosine binds. The N-terminal lobe comprises of a five-stranded anti-parallel β-sheet and a single α-helix connecting the strands β3–β4. The C-terminal lobe is mainly α-helical. The C-terminal lobe contains the substrate-binding site located in a groove on its surface [57]. A glycine-rich loop, containing the consensus kinase sequence Gly–x–Gly–x–x–Gly (residues Gly43–Gly48), and the hinge region (residues Met104–Ser111) surround the catalytically active site of TAK1. Adenosine binds to the TAK1 kinase domain at the interface of the N- and the C-terminal lobes, with the purine base forming two hydrogen bonds with the hinge region. One hydrogen bond is formed with the amide nitrogen atom of Ala107 and the second hydrogen bond is formed with the carbonyl oxygen atom of Glu105 [57]. It has also been shown that the residues 480–504, encompassing the TAB1 C-terminal region, are adequate for TAK1 binding and activation [38]. Truncation analysis of TAB1 has revealed that a 30 amino acid residue sequence in TAB1 containing a α-helical region is indispensable for TAK1 binding under physiological conditions [42]. Crystallization and expression of a chimeric protein in which the C-terminal 36 residues

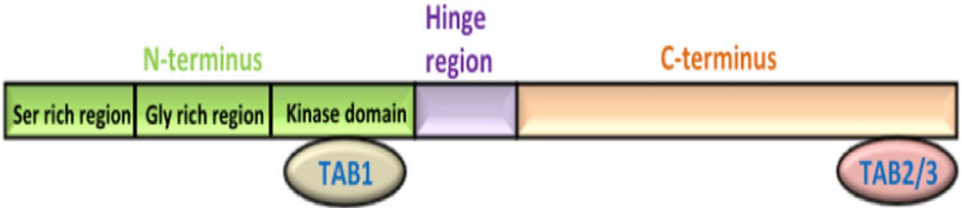

Fig. 1 Schematic representation of TAK1domain structure and the binding sites for various TAK1 binding proteins

of TAK1 were swapped with 36 amino acid residues of at TAB1 C-terminus revealed that TAB1 and TAK1 interact via a binding pocket present on the catalytic domain of TAK1. This interaction utilizes the distinct property of hydrophobicity in the α-helix of TAK1 activating domain of TAB1 [57]. The TAK1 activating domain of TAB1 consists of three regions: an ordered loop spanning from Histidine 468 to Proline 480, a short turn encompassing the region from Tyrosine 481 to Phenylalanine 484 and a α-helix spanning the region from Alanine 485 to Aspartate 494. The α-helix assures the apt arrangement of a motif of aromatic amino acids whose hydrophobicity and morphology closely complements the hydrophobicity and shape of the TAB1 binding pocket in TAK1. The α-helix has the sequence, in which the aromatic amino acids are crucial for hydrophobicity. The residues in the α-helix form a ladder in which the side chains of aromatic amino acids clamp into the TAB1 binding region in the kinase domain of TAK1 and mount the hydrophilic residues to the exterior of the helix [57]. Mutational analysis has also revealed that Phenylalanine 484 and Tyrosine 488 in TAB1 are crucial for TAK1 binding [42]. These residues are involved in substantial lipophilic associations within the TAB1 binding pocket and hence are essential in stabilizing the TAK1/TAB1 complex. The interaction between TAK1 and TAB1 appears to be a locking mechanism [57]. The chimeric protein of TAK1/TAB1 (Ile31–Gln304:His468–Pro405) remains enzymatically active, however, it exhibits no phosphorylation on Thr-184, Thr-187 and Ser-192 of TAK1. Hence the phosphorylation at these sites is not mandatory for TAB1 binding to TAK1. Also the binding of TAB1 appears to be sufficient for activating TAK1 even in the absence of these phosphorylations [57].

Regulation of TAK1 activity

TAK1 kinase activity is regulated via a variety of post-translational modifications including phosphorylation and poly-ubiquitination. Since the phosphorylation of TAK1 at Thr-187 is crucial for its kinase activity in the TNF receptor (TNFR) signaling, methylation and ubiquitination are also crucial in regulating its activity [44]. Many studies have shown that site-specific phosphorylation and ubiquitination on TAK1 are important in regulating TAK1 activity [24]. Moreover, full activation of TAK1 requires *O*-linked β-*N*-acetylglucosaminylation (O-GlcNAcylation) of TAB1 at Ser-395 [58].

While considerable progress has been made in unraveling the molecular events linking the activated TGF-β receptor mediated R-Smad activation, molecular events that mediate the activation of non-Smad signaling molecules however remain poorly understood. The activation mechanism of TAK1 is remarkably different from that of the activation mechanism of Smad2/3. TGF-β1 induced activation of Smad2/3 involves docking of Smad2/3 to TβRI followed by phosphorylation of these Smads by the kinase activity of TβRI [59, 60]. However TGF-β1-induced activation of TAK1 occurs via an independent mechanism and does not require TβRI kinase activity [19, 34]. Phosphorylated Smad2/3 are then released from the receptor complex and are free to interact with Smad4 to relay TGF-β1 signal onwards. On the other hand, TAK1 stably associates with TβRI in the absence of ligand stimulation in glomerular mesangial cells. After ligand stimulation of TβRI, it forms a heterodimer with TβRII which is followed by dissociation of TAK1 from the TβRI–TβRII complex. After dissociation TAK1 interacts with TAB1 and is activated by TAB1-mediated autophosphorylation [19].

Regulation by ubiquitination

One of the mechanisms in the post-translational modification of proteins is ubiquitination, which controls the activity and half-life of many proteins [61]. Although TAB1 is vital for TGF-β1-induced activation of TAK1 in glomerular mesangial cells, TAB1 by itself does not interact with TGF-β receptors and is not required for TAK1 and TβRI interaction. The interaction between TAK1 and TβRI requires TAB2 and another adaptor protein TRAF6 (TNF receptor-associated factor 6) to induce TAK1 activation in glomerular mesangial cells [19]. LPS and IL-1 activate TAK1 by forming Lys63 linked poly-ubiquitinated TRAF6 which then interacts with the ring finger domain of TAB2 and TAB3 [53].

TRAF6, a ubiquitin ligase (E3), is a member of a family of RING (really interesting new gene) domain ubiquitin ligases catalyzing the synthesis of polyubiquitin chains linked via Lys-63 of ubiquitin. The highly conserved ubiquitin-binding zinc finger domain in TAB2 binds preferentially to Lys-63-linked polyubiquitin chains on TRAF6 and encourages TGF-β1-induced activation of TAK1 [34, 49, 62]. TβRI possesses a consensus-binding site (basic residue-X–P–X–E–X–X– aromatic/acidic residue) for TRAF6 and evidences unveil that TRAF6 physically interacts with TβRI and stimulate Lys-63-dependent poly-ubiquitination of TAK1 at Lys-34 activating TAK1 in the process [34, 49, 62, 63]. Recent studies have claimed that the poly-ubiquitination target site of TRAF6 for TAK1 activation is Lys-158 instead of Lys-34, however, the reason for this inconsistency in poly-ubiquitination site on TAK1 remains unclear [64–66]. Thus, the kinase activity of TβRI is a prerequisite for activation of the canonical Smad signaling pathway, whereas ubiquitin ligase activity of TRAF6 mediates the activation of TAK1 in a receptor kinase-independent manner. TGF-β1 particularly activates TAK1 via the interaction of TβRI with TRAF6, however, Smad activation does not depend on TRAF6.

TAK1 has been shown to be essential for IL-1-mediated activation of NF-κB, JNK, and p38 [25, 28, 53, 67]. After binding of IL-1 to the ligand binding domain of the IL-1 receptor, an adaptor protein MyD88 (myeloid differentiation factor 88) gets docked to the IL-1·IL-1R complex, which then leads to the docking of the IL-1R-associated kinases and TRAF6 (tumor necrosis factor receptor-associated factor 6) to activate TAK1 [68–70]. After activation, TAK1 translocates from the membrane to cytosol along with TRAF6 and its binding partners, TAB1 (TAK1-binding protein 1), TAB2 and TAB3 [23, 39, 40, 52]. After activation TAK1 further leads to the phosphorylation and activation of IκB kinase (IKK), c-Jun NH2-terminal kinase (JNK) and p38 [28, 53].

Regulation by phosphorylation

The activation loop of serine/threonine protein kinases contains a number of pivotal serine and threonine residues and phosphorylation of these critical serine and threonine residues are essential for kinase activation. Dephosphorylation of these residues renders these kinases inactive [71, 72]. Diverse studies have shown that replacement of these residues with acidic residues to mimic the phosphorylation state renders these kinases constitutively active [73, 74]. A number of studies have been carried out to identify the phosphorylation sites on TAK1 and to analyze the effect of these phosphorylations on the kinase activity of TAK1. Mutation analysis of the phosphorylation sites in the activation segment of TAK1 has revealed that autophosphorylation at Ser-192 precedes TAB1 phosphorylation and is followed by sequential phosphorylation at Thr-178, Thr-187, and finally Thr-184 [75]. Phosphorylation of TAK1 at Thr-184 and Thr-187 located in the kinase domain of TAK1 is essential for TAK1 kinase activity [44, 75]. However, a few researchers have suggested that the phosphorylation of TAK1 at Thr-187 is not sufficient for its activation [38, 43, 51, 76] and additional post-translational modifications are needed for full activation. A number of phosphorylation sites are present outside the kinase activation loop of TAK1 [77–79]. However, the role of these phosphorylations continues to remain unclear.

Tumor necrosis factor-α has been shown to stimulate the phosphorylation of TAK1 at Thr-187 and Ser-192. Substitution of these residues with the acidic amino acids culminates in inactivating the kinase rather than making the kinase constitutively active [38, 43, 44, 51]. Also Thr-178 and Thr-184 residues within the kinase activation loop of TAK1 are crucial regulatory phosphorylation sites for TAK1 induced NF-κB and AP-1 activation. Phosphorylation of the two threonine residues within the kinase activation loop is an established mechanism for TAK1-mediated NF-κB and AP-1 activation. Hence four conserved serine/threonine residues within the activation loop of TAK1 are phosphorylated during the activation process. However, replacement of Thr-178 and Thr-184 but not Thr-187 and Ser-192 with acidic residues renders TAK1 active in a TAB1-dependent manner [76].

A number of kinases are phosphorylated within kinase activation loop located between the conserved sequence DFG in kinase subdomain VII and APE in kinase subdomain VIII [72]. The activation loop is critical for recognition of substrate. Phosphorylation within this loop is important to permit correct orientation of the substrates to the catalytic site. Most of the times, the upstream kinases in the kinase cascades are responsible for phosphorylations in the activation loop of these kinases [80]. However, in some cases, stimuli-dependent conformational change mediates autophosphorylation in this segment [81–83]. The phosphorylation sites within the kinase activation loop of TAK1 include Thr-184, Thr-187, and Ser-192. The presence of pro-inflammatory cytokines increases TAK1 phosphorylation within the activation loop [38, 43]. However the catalytic activity of TAK1 is required for this phosphorylation to occur, which is indicative of the fact that TAK1 autophosphorylates its activation loop. Upon stimulation by cytokines, probably TAK1 autophosphorylation is facilitated through the conformational change induced by the assembly of a signaling complex, which leads to conversion of TAK1 into catalytically active form. It has been established that among the phosphorylation sites in TAK1, the one at Thr-187 harmonizes with TAK1 activation [44].

The mechanisms by which MAPKKKs are activated have been elucidated. Mostly the activation mechanisms involve phosphorylation of MAPKKKs. In some cases, autophosphorylation of MAPKKKs seems to be responsible for activation. However in some signaling pathways, other protein kinases such as Ste20-like MAPKKKKs phosphorylate and activate MAPKKKs. For IL-1- and TAB1-induced activation of TAK1, auto-phosphorylation of TAK1 at Ser-192 is important. Substitution of Ser-192 to Ala, abrogates both IL-1- and TAB1-induced phosphorylation of TAK1. Moreover, this mutation produces a kinase-dead form of TAK1 that impedes its ability to phosphorylate exogenous substrates or to activate NF-κB. Based on these evidences, it is presumed that Ser-192 is the auto-phosphorylation site in TAK1 and is crucial for catalytic activity of TAK1. Additionally, replacement of Ser-192 with glutamic acid or aspartic acid residues, instead of boosting the kinase activity of TAK1, renders the enzyme inactive [43]. Research based evidences have reported similar observations in analogous mutants of MEK5, MKK4, and MEKK1 [81, 84].

Upon stimulation by IL-1 TAK1 is activated by autophosphorylation at Ser 192. In absence of IL-1 stimulation endogenous TAK1 remains constitutively associated with TAB1, however, it remains unphosphorylated and inactive,

suggesting that binding of TAB1 to TAK1 is not adequate to induce phosphorylation and hence activation of endogenous TAK1 in vivo. However, in absence of IL-1 stimulation, ectopically expressed TAK1 is activated by co-expression with TAB1. Moreover, the incubation of endogenous TAK1·TAB1 complexes prepared from unstimulated cells, with ATP results in phosphorylation of TAK1 at Ser 192 and activation of TAK1. Hence, binding of TAK1 to TAB1 appears to be adequate for activation of TAK1 in vitro. These results however raise the possibility that a putative inhibitory factor blocks the activity of the endogenous TAK1·TAB1 complex in the absence of IL-1 stimulation. IL-1 treatment may however disrupt this inhibitory regulation and thereby allow auto-phosphorylation of TAK1 at Ser 192 and subsequent activation of TAK1 [43].

HGK, a Ste20-like MAPKKKK, is a serine threonine kinase, and has been implicated in the activation of TAK1 leading to JNK activation. HGK-induced activation of JNK is occluded by a kinase-dead mutant of TAK1, however the kinase-dead mutant of MEKK1 does not inhibit HGK induced JNK activation. HGK is activated by TNF and UV irradiation, suggesting that HGK may play its role as an upstream kinase of TAK1 in these signaling pathways [85]. TAK1 is activated by a variety of extracellular stimuli, including transforming growth factor-β, TNF, IL-1 and environmental stresses, suggesting that TAK1 is regulated by many different mechanisms [27]. TAK1 may hence be activated by TNF via HGK mediated phosphorylation, whereas IL-1 mediates TAK1 activation by auto-phosphorylating it.

TAK1 also dimerizes through its C-terminal coiled-coil domain, which is required for auto-phosphorylation of TAK1 at Thr-187 in its kinase domain [86]. TAK1 is also phosphorylated at Ser-412 and phosphorylation at this residue is important for TAK1 kinase activation in IL-1R and TLR signaling pathways. This regulation is conserved in evolution, as evidenced by studies using zebrafish embryos. It has been established that the PKA kinase family members PKACα and PRKX are responsible for phosphorylating TAK1 at Ser-412. In vitro studies have shown that these kinases work independently of each other and either one could phosphorylate TAK1 at Ser-412. Interestingly, however a single knockdown of PKACα or PRKX or a double knockdown of both PKACα and PRKX stemmed in aberrant Ser-412 phosphorylation to a hard-to-detectable level in vivo, indicating that neither PKACα nor PRKX alone was sufficient to bring Ser412 phosphorylation. Whether TAK1 Ser-412 phosphorylation occurs and is important for function in pathways other than IL-1R and TLR pathways requires further investigation. Ser-412 is present at the C-terminus of TAK1, which is far from the kinase domain. This kind of mechanism is not unique to TAK1. Kinases in the Akt, NDR, and PKC families also require the phosphorylation of Ser/Thr residues outside their respective kinase domains [86].

Regulation by dephosphorylation

Deactivation of TAK1 is also a pivotal mechanism in regulating TAK1 kinase activity. The extent to which a protein gets phosphorylated is regulated by the balanced activities of protein phosphatases and protein kinases. In unstimulated state, TAK1 kinase activity is regulated by protein phosphatase PP2C family members [87, 88]. Protein phosphatase 6 (PP6), a protein phosphatase 2C family member rapidly dephosphorylates TAK1 at Thr-187, which is a critical site for auto-phosphorylation [89]. PP6 is activated through its binding to the K63 linked polyubiquitin chains of TAB2. PP6 hence cannot dephosphorylate TAK1 in absence of TAB2 thus increasing TAK1 and JNK phosphorylation [90]. TAB2 thus mediates not only the phosphorylation, but also the dephosphorylation of TAK1 through PP6. The inhibition of type 2A protein phosphatases culminates in hyperphosphorylation and hyperactivation of TAK1 following stimulation by IL-1 [89].

The dephosphorylation and inactivation of TAK1 is mediated by both PP2C and PP6. However the site(s) dephosphorylated by PP2C has not yet been elucidated. Since the activity of TAK1 is dependent on phosphorylations at Thr-184, Thr-187, and Ser-192 in its activation loop, it seems that both PP2C and PP6 dephosphorylate these sites. It has been seen that PP6 associates constitutively with TAK1, however PP2C dissociates from TAK1 upon stimulation by IL-1 [88, 89], suggesting that PP2C inhibits the activity of TAK1 in the unstimulated state and release of PP2C from TAK1 complex may assist in activation of TAK1. It has been shown that knock down of PP6 affects only the activation of TAK1 following IL-1 stimulation but it does not affect the basal activity of TAK1. PP6 is therefore fundamentally involved in down-regulating activated forms of TAK1 produced after stimulation [89]. Both PP6 and PP2C therefore regulate the activity of TAK1 by dephosphorylation, but they appear to function on different forms of TAK1.

The dissociation of TAK1 from the TRAF6-complex also inactivates TAK1 by inducing a conformational change in TAK1, converting it to an inactive state, thereby blocking further autophosphorylation of TAK1 [91]. The degree of TAK1 activation is also controlled by a feedback mechanism in which TAK1 is downregulated by p38α MAPK. This mechanism involves the p38α-mediated phosphorylation of TAB1 at two residues, Ser423 and Thr431 and phosphorylation of TAB2 and TAB3 at unknown sites, which stimulates dephosphorylation of TAK1 [40, 92]. Hence the activation of TAK1 by LPS, TNF-α or IL-1 can be increased by treating the cells with p38α inhibitors or in cells that lack p38α.

However the inhibition of p38α results in the enhanced activation of JNK and NF-κB [92].

Regulation by deubiquitination

Deubiquitinases A20 and CYLD form complexes with ITCH, an E3 ubiquitin ligase and catalyze the cleavage of K63-linked polyubiquitin chains [93]. The A20-ITCH or CYLD-ITCH complex mediate the cleavage of K63-linked polyubiquitin chains on catalytically active TAK1 and also mediates K48-linked ubiquitination to abort TAK1 mediated activation of NF-κB via degradation of TAK1 by proteosomal pathway [94, 95]. NF-κB activates the deubiquitinases A20 and Cezanne, but not CYLD, to negatively regulate the activity of TAK1 and NF-κB by dislodging K63 polyubiquitin chains [96]. Another deubiquitinase, ubiquitin-specific peptidase 4 (USP4) cleaves the K63 polyubiquitin chains conjugated to K158 of TAK1 and downregulates the TNF-α induced activation of TAK1. In HeLa cells the knockdown of USP4 promotes the TNF-α induced polyubiquitination of TAK1 [97].

TAK1 and the energy sensing AMPK pathway

Discovered by its potential to phosphorylate and inactivate the key enzymes of lipid metabolism i.e. HMG coA Reductase and Acetyl coA carboxylase, AMPK is acknowledged to have multiple downstream effectors [98–100]. AMP-activated protein kinase has a vital role in regulating the metabolism of lipids and glucose, maintaining energy homeostasis of cells, and regulation of stress responses of cells [101, 102]. AMPK is responsible for perceiving the intracellular ratio of AMP to ATP, an index of the cellular energy balance [103]. An increase in the ratio of AMP to ATP following certain stresses that drain the ATP levels of the cell lead to AMPK activation [104, 105]. Activation is triggered by the allosteric stimulation of AMPK by AMP binding and through the release of ATP to relieve the inhibition [106]. Upon binding of AMP or ADP to AMPK, a conformational change occurs in AMPK that stimulates its phosphorylation by upstream kinases and discourage the dephosphorylation by phosphatases [107–109]. The upstream kinase (AMPK Kinase) that mediates the phosphorylation of AMPK is also activated by AMPK [110, 111]. However in some tissues like skeletal muscle, the ratio of creatine to phosphocreatine, again reflecting the energy status of the cell, regulates AMPK activity [112]. After activation AMPK responds to the reduced energy availability (high cellular ratio of AMP:ATP) by boosting ATP generating processes like fatty acid oxidation and glucose transport and inhibiting ATP-consuming processes that are not critical for cell survival like cell proliferation and growth and lipid and protein synthesis [102, 105, 113]. Besides energy levels, AMPK is also regulated by leptin, gherlin and adiponectin [114–116]. AMPK also plays a vital role in regulating food intake and appetite [115, 117]. AMPK serves as an essential therapeutic target for type 2 diabetes in humans [102, 118]. Snf1 protein kinase is the homolog of AMPK in S.cerevisae [119–121]. Snf1 is actually the catalytic subunit (α) of a heterotrimeric protein complex, which besides Snf1 also contains one of the β-subunits (Sip1, Sip2, or Gal83) and a γ-subunit Snf4 [122, 123]. Snf1 contains 633 amino acids with a kinase domain spanning 330 amino acids near its amino terminus. The C-terminus of Snf1 accommodates a regulatory region important for binding to other subunits of the heterotrimeric complex [124]. The β-subunits of the complex regulates the cytoplasmic and nuclear localization of the complex [125].

The kinases activating AMPK are immensely conserved between mammals and yeast. Three homologous kinases phosphorylate the activation loop of Snf1 catalytic subunit at Thr-210, and these include Sak1 (Snf1-activating kinase, previously Pak1), Elm1 and Tos1 [126–128]. The mammalian counterparts of Snf1 kinases include LKB1 (liver kinase B1) and Ca^{2+}/calmodulin-dependent protein kinase kinase (CaMKK) and these phosphorylate the activation loop of AMPK catalytic subunit at Thr-172 and activate AMPK both in vitro and in vivo [126, 129, 130]. The mammalian and yeast kinases exhibit strong exchangeable functionality. In vitro studies have shown that Elm1 and Tos3, the yeast Snf1 kinases, phosphorylate and activate AMPK [126, 128]. CAMKK and LKB1 also phosphorylate and activate the yeast Snf1 endowing Snf + growth phenotype to sak1Δ tos3Δ elm1Δ mutant strains of yeast [130, 131].

The most interesting question regarding the role of TAK1 is in the regulation of AMPK activity. TAK1 is established as an upstream AMPK kinase in a screen utilizing yeast mutants lacking the upstream kinases of Snf1 (the yeast homolog of mammalian AMPK). Recombination studies have shown that TAK1–TAB1 phosphorylates AMPK α-catalytic subunit at Thr-172 in vitro. Also the overexpression of TAK1 and TAB1 enhances the phosphorylation of AMPK in HeLa cells [132]. Transgenic mice expressing dominant negative TAK1 had abnormalities in heart resembling the Wolff-Parkinson-White syndrome, which is triggered by mutations in AMPK [37]. Certain stresses such as osmotic shock and hypoxia, which are the eminent activators of AMPK, also lead to the activation of TAK1 [45, 133]. Furthermore the stimulatory effects of TNF-α, IL-1 and TGF-β on AMPK phosphorylation also suggest TAK1 as a possible kinase of AMPK [132, 134]. However, when compared with CaMKII and liver kinase B1 (LKB1) the prime AMPK kinases, TAK1 may only play subsidiary role in AMPK activation. Also the knock down of TAK1 in MEF's renders the cells unable to activate in response to metformin, oligomycin and 5-aminoimidazole-4-carboxamide riboside.

Since these drugs fail to activate LKB1, the AMPK kinase, it was advocated that TAK1 may function upstream of LKB1 rather than a direct kinase of AMPK [37]. It has been shown that the genetic inactivation of TAK1 hinders the phosphorylation of AMPK. Also in myocardium the TAK1 binding partner, TAB1 is complexed with AMPK advocating interplay between the two kinases [135]. Since there is no potential tie-up between LKB1 or other AMPK kinases and TAK1, the deletion of TAK1 results in defective liver kinase β1 activation in mouse embryo fibroblasts suggesting other possible mechanisms in addition to or instead of TAK1 directly phosphorylating AMPK [37] (Fig. 2).

TAK1 and autophagy

Autophagy is an evolutionarily conserved, non-selective intracellular deterioration mechanism during which the cytoplasmic contents are delivered to the lysosome for degradation. The process of autophagy plays diverse characters in cell, mediating both cell death and cell survival. During nutrient starvation, autophagy is activated to supply essential nutrients to the cell. However under other instances it can serve as a process contributing to cell death known as autophagic cell death [136, 137]. TAK1 has recently emerged as a molecule regulating cellular autophagy. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) promotes cellular autophagy by activating TAK1 rapidly and in a dose dependent manner. The induction of autophagy by TRIAL is mediated by AMPK. Activation of AMPK by TRIAL is independent of CaMKKβ and LKB1 but depends on TAK1 and TAB2. TRIAL activates TAK1, which in turn leads to the activation of AMPK, responsible for inhibiting mTORC1, a dynamic autophagy inhibitor. The induction of autophagy and activation of AMPK by ionomycin and starvation is inhibited by depletion of CaMKKβ and LKB1 respectively. Also, the expression of the dominant negative mutant of TAK1 in MEF's diminished the TRIAL induced AMPK activation compared to the WT-MEF's and also sensitized the cells to TRIAL-induced cell death [138]. These findings suggest the role of TAK1 as an AMPK activator and hence an autophagy inducer.

AMPK, an energy sensing evolutionary conserved kinase and a key regulator of energy balance of cell has recently unfolded as a conjectural agent in activating cellular autophagy. AMPK induces autophagy by directly phosphorylating ULK1, a mammalian homolog of Atg1 [139]. TRIAL, a TAK1 and hence an AMPK activator, inhibits mTORC1 and hence the phosphorylation of S6K1. TRIAL hinders the phosphorylation of S6K1 as potently as rapamycin, a well-established and direct mTORC1 inhibitor [138]. Two glaring mechanisms are responsible for inhibition of mTORC1 and autophagy induction by AMPK.

- Phosphorylation of tuberous sclerosis complex 2 (TSC2) at Ser 1387 by AMPK leads to activation of TSC2 [140]. Activation of TSC2 in turn leads to the inhibition of RHEB, a ras-family GTP-binding protein and an activator of mTORC1 complex (Fig. 3).
- Phosphorylation of raptor, a substrate binding subunit of mTORC1 by AMPK stimulates the binding of raptor to 14-3-3 proteins resulting in the inability of mTORC1 to bind its substrates [141] (Fig. 4).

TAK1 has also been shown to inhibit the phosphorylation of S6K1 [142]. Under normal nutritional conditions,

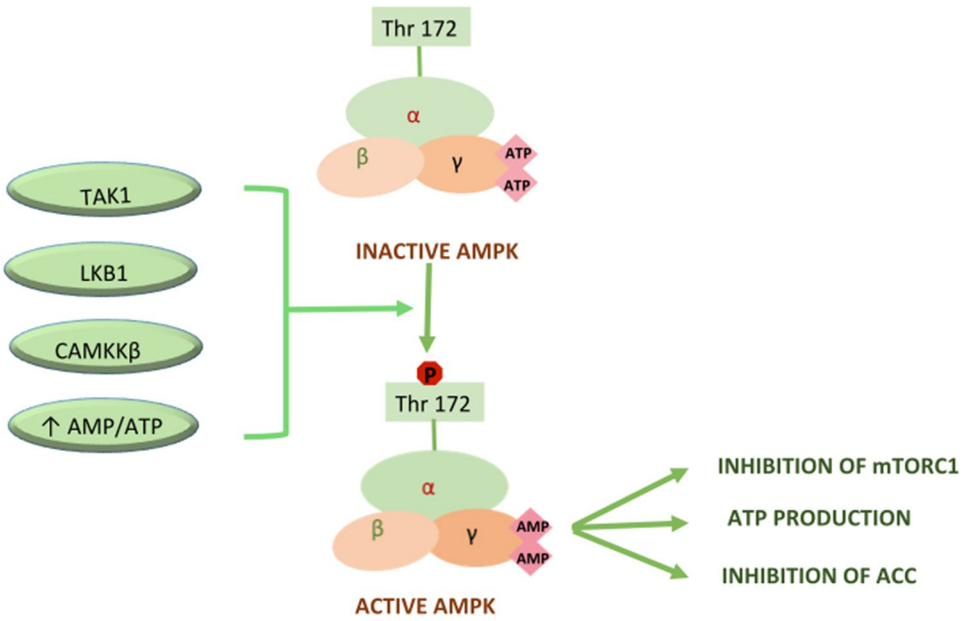

Fig. 2 Phosphorylation of AMPK by various kinases

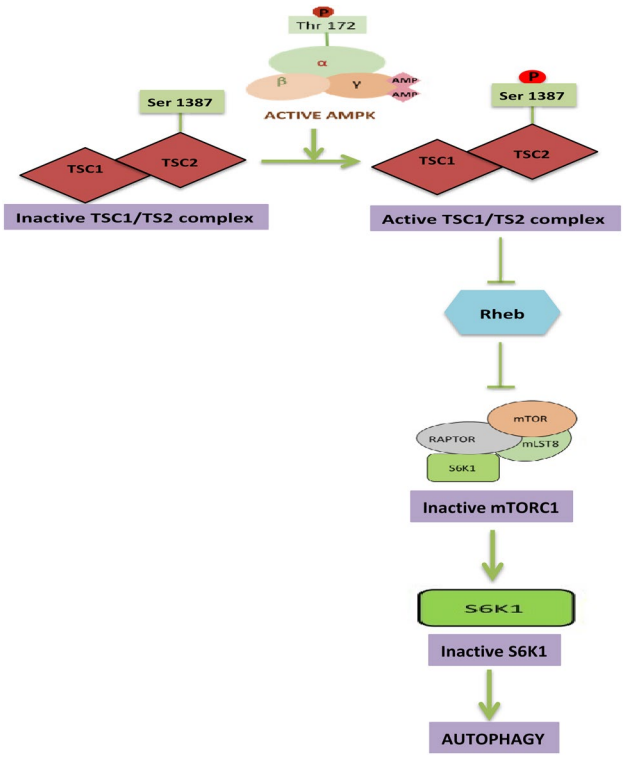

Fig. 3 TAK1 activates AMPK, which subsequently activates TSC1/TSC2 complex and inhibits mTORC1 complex as a consequence

downregulating the phosphorylation of S6K1 is associated with induction of autophagy (cytotoxic autophagy). TAK1 hence, induces autophagy by inhibiting S6K1 phosphorylation. S6K1 plays a dual role in regulating autophagy. It negatively regulates autophagy under normal nutritional conditions [143, 144]. However during starvation, S6K1 positively regulates autophagy [143, 145]. Ionizing radiations also promote autophagy by reducing the phosphorylation of S6K1 [147]. Furthermore, pentagalloyl glucose diminishes the phosphorylation of S6K1 and induces autophagy in a caspase independent manner [146].

TAK1 and mTOR crosstalk

Target of rapamycin (TOR) is an evolutionary conserved kinase that serves as an environmental transducer of signals emanating from nutrient levels in unicellular organisms. In multicellular organisms TOR responds to a variety of environmental signals, such as growth factors, mitogens and hormones, enabling this kinase to coordinate a multitude of cellular functions [147, 148]. TOR and its mammalian isoform, mTOR, belong to the PI3K related protein kinase family [148].The TOR proteins are distinct among the PI3K related protein kinase family in that they directly bind to rapamycin via the rapamycin binding domain FKBP12. TOR exists in two functional complexes, TOR complex 1 (TORC1) and TOR complex 2 (TORC2), that are conserved from yeast to mammals and each catalyzes the phosphorylation of different sets of substrates [149, 150]. These complexes vary in their subunit composition, substrate specificity, regulation and rapamycin sensitivity. TORC1 is composed of mTOR, GβL [151], and raptor [152, 153]. TORC1 suppresses catabolic processes, promotes a wide array of anabolic processes and displays acute rapamycin sensitivity [154]. Mammalian TORC1 (mTORC1) has a primary function in autophagy regulation [155]. TORC2 composed of mTOR, GβL (154), and rictor [156], is insensitive to rapamycin and promotes cell survival and proliferation [154]. Msin1 and Protor-2 are also the mTORC2 associated proteins [157, 158]. The activity of the TOR complexes is regulated by endogenous inhibitors that include PRAS40 and FKBP38 for mTORC1, however the exchange factor found in platelet, leukemic and neuronal tissue serves as a negative regulator for mTORC2 [159–161]. DEPTOR, a DEP-domain containing mTOR

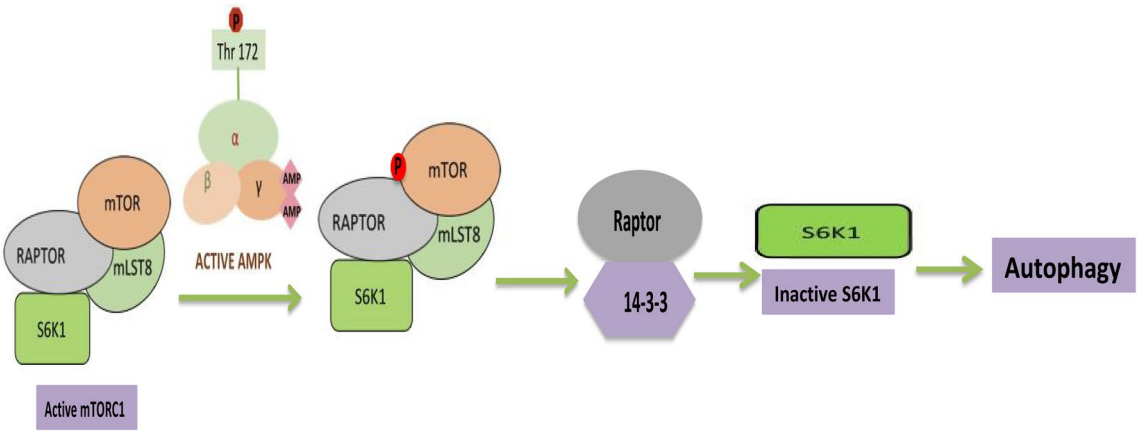

Fig. 4 TAK1 activates AMPK, which stimulates the phosphorylation of raptor and its binding to 14-3-3

interacting protein binds to both the TOR complexes to regulate their activities [162].

Raptor [regulatory-associated protein of mammalian target of rapamycin (mTOR)], is a 150 kDa protein that constitutively associates with mTORC1 and is essential for its activity [153]. Raptor binding to mTOR requires multiple sites along the length of raptor. It binds primarily but not solely to the amino terminal region of mTOR [152]. Raptor in addition to providing the substrate binding specificity to mTORC1 also plays a role in regulating the response of mTORC1 to nutrients and growth factors [152, 153]. Raptor acts as a scaffold protein for the recruitment of mTOR to its substrates p70S6K and 4EBP-1. Raptor rather than changing the catalytic activity of mTOR binds to p70S6K and 4EBP-1, apposes them to mTOR and increases the mTOR catalyzed phosphorylations of 4EBP-1 and p70S6K1 [152, 153, 163]. The binding of mTOR substrates (p70S6K and 4EBP-1) to raptor requires a short binding sequence, the TOS (TOR signaling) motif [164]. Mutational analysis have shown that the mutation of the TOS motif in 4E-BP1 dramatically inhibits its phosphorylations in vivo [164] and entirely eliminates the mTOR catalyzed phosphorylations of 4EBP-1 in vitro [163, 165, 166]. However deleting or mutating the TOS motif of p70S6K drastically inhibits its activating phosphorylation and activity [164, 167].

After stimulation by insulin, PRAS40, a competitive inhibitor of mTORC1, dissociates from raptor and the binding of mTORC1 substrates (4E-BP1 and S6K) is facilitated [168, 169]. TOR Signaling motif (TOS motif), a consensus sequence present in PRAS40 and mTORC1 substrates (4E-BP1 and S6K1) is responsible for their binding to raptor [164, 165, 169, 170]. The potential of raptor, the substrate specificity component of mTORC1, to present the substrates (4E-BP1 and S6K) to the catalytic component of TORC1, is mandatory for the phosphorylations catalyzed by TORC1 [153].

S6 kinase 1 (S6K1), a translational regulator protein is the best characterized effector of mTORC1 signaling [152]. In vitro studies have shown that mTORC1 phosphorylates S6K1 at threonine 389 (Thr389), a key residue within the hydrophobic motif carboxy terminal to the kinase domain [171]. The treatment of cells with rapamycin elicits rapid dephosphorylation of S6K1 at Thr-389 and leads to its inactivation [172–174]. Since phosphorylation of S6K1 at Thr-389 is sensitive to rapamycin and mTORC1 phosphorylates S6K1 at the same site in vitro, hence it has been proposed that mTORC1 is the physiological Thr-389 kinase regulating S6K1 activity [175]. S6K1 has a vital role in regulation of protein synthesis, cellular growth and proliferation [176, 177]. Besides playing a major role in regulating cell size, S6K1 is also implicated in regulating autophagy [178, 179]. S6K1 can act as a positive or negative regulator of autophagy depending upon the nutritional conditions. Under the conditions of starvation, S6K1 positively regulates autophagy (cytoprotective autophagy), however, under normal nutritional conditions S6K1 inhibits autophagy (autophagic cell death) [143, 145]. Inhibition of mTORC1 signaling is the distinctive indicator of autophagy but how mTORC1 signaling is regulated during autophagy is the intriguing question. S6K1 impedes autophagy in mammalian cells, and the phosphorylation status of S6K1 harmonizes with autophagy inhibition [180, 181].

Immunoprecipitation experiments have revealed that TAK1 binds to S6K1, and the truncation of the carboxy terminal domain of S6K1 abrogates the interaction suggesting that the carboxy terminal domain of S6K1 is involved in binding TAK1. The binding of TAK1 to S6K1 reduces the phosphorylation of S6K1. Research based evidences have demonstrated that TAK1 interacts with Raptor and co-expression of TAK1 triggers a decrease in the binding of S6K1 to raptor. Moreover the binding of S6K1 to raptor increases in raptor dose dependent fashion. TAK1 hence competes with S6K1 for raptor binding thereby inhibiting the phosphorylation and activation of S6K1 [142]. S6K1 has also been found to intrude the binding of TAB1 to TAK1, and hence has been implicated in regulating the TLR signaling negatively. S6K1 has been shown to interact with the amino terminal domain of TAK1. The amino terminal domain of TAK1 is also responsible for its interaction with TAB1. Also, the interaction of TAK1 with S6K1 or TAB1 is remarkably abolished in presence of TAB1 or S6K1 respectively. These findings clearly evince that the amino terminus of TAK1 is involved in binding S6K1, and this partnership negatively regulates TAK1 activation by competing TAK1–TAB1 interaction [182]. By interrupting the interaction between TAK1 and TAB1, S6K1 may also enervate the AP-1 activating MAP Kinase pathway, as TAB1 is the molecule responsible for recruitment of p38 MAPK to TAK1 complex [58, 183]. The interaction between TAK1 and S6K1 thus seems to be momentous in TAK1 signaling for both AP-1 activation and NF-κB activation via the JNK pathway and IKK pathway respectively. S6K1 thus, regulates the TLR-2 and TLR-4 mediated signaling pathways in a negative manner [182]. It has been well revealed that the deficiency of S6K1 results in the enhancement of the kinase activity of TAK1, increases the activation of downstream molecules of TAK1 and boosts NF-κB dependent gene expression upon TLR-2 or TLR-4 stimulation. S6K1 deficiency also results in the enhanced production of pro-inflammatory cytokines including IL-1β, IL-6 and TNF-α. Conversely, the overexpression of S6K1 vanquishes the production of pro-inflammatory cytokines and also subjugates NF-κB activity [182] (Figs. 5, 6).

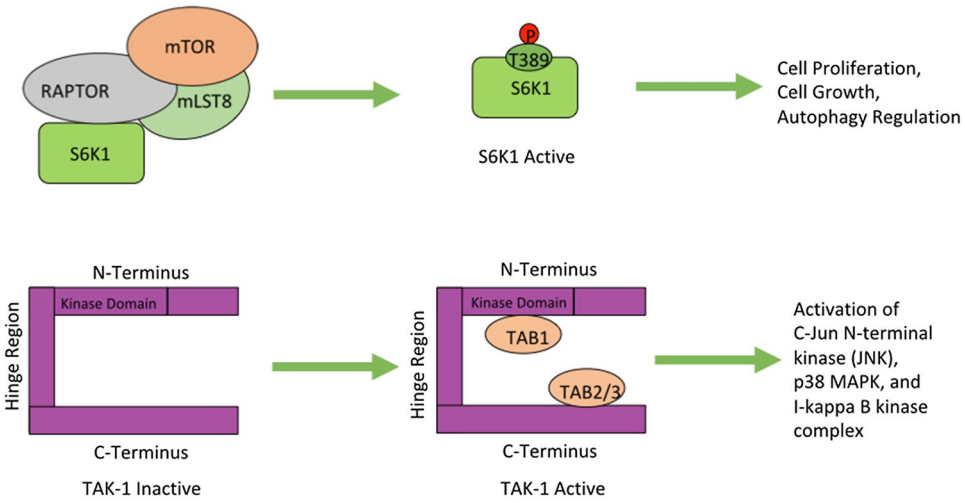

Fig. 5 Activation of S6K1 and TAK1 by mTORC1 and TAK1 binding proteins respectively

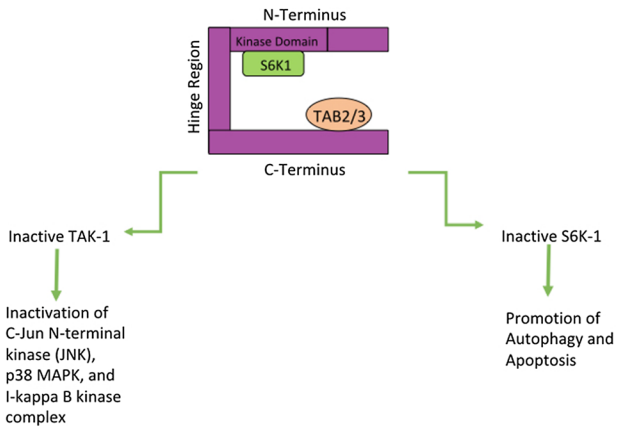

Fig. 6 Antagonistic behavior of S6K1 and TAK1 respectively

TAK1 and apoptosis

Programmed cell death, also called as apoptosis, is a physiological process of shedding cells and has a pivotal role in removing unwanted and damaged cells. It also has a vital role in normal development. On the other hand abandoned cell death leads to diverse disease in humans. Hence, the meticulous cognizance of the underlying molecular mechanisms of cell death is crucial in understanding molecular pathogenesis of disease. TAK1 has recently emerged as a key molecule in dictating cell fate. TAK1 has a dynamic role in activating the NF-κB pathway. This pathway has innumerable target genes, known to foster cell proliferation, trigger inflammation and obstruct apoptosis [184–186]. NF-κB has also been shown to encourage angiogenesis and facilitate metastasis and invasion. NF-κB has also been shown to facilitate epithelial to mesenchymal transition (EMT) and hence promote distant metastasis [187].

BMP-2 has been shown to induce apoptosis in MH60 cells. BMP-2 promotes apoptosis by activating TAK1 thereby phosphorylating and activating p38- stress activated protein kinase. However, the expression of the kinase dead mutant of TAK1 in these cells impedes apoptosis mediated by BMP-2, evincing BMP-2 induced apoptosis occurs through TAK1-P38 pathway in these cells. The ectopic expression of Smad6 in MH60 cells renders them resistant to BMP-2 induced apoptosis. Smad6 expression discourages the activation of TAK1 and hence phosphorylation of p38. Smad6 interacts with TAK1 and negatively regulates TAK1 pathway in BMP-2 signaling cascade [188].

Recent studies have also shown that TAK1 endorses cell survival in HeLa cells that have either been irradiated or exposed to hypothermia [189]. So, blocking TAK1 activity may stimulate cell death. 5Z-7-oxozeaenol, which is a puissant inhibitor of TAK1 sensitizes both MEF and HeLa cells to etoposide, doxorubicin and TNF-α induced cell death [190]. Also treatment of A549 cells with 5Z-7-oxozeaenol results in reduced production of Bcl-2 after exposure to hyperthermia and a perceptible increase in hyperthermia induced loss of mitochondrial membrane potential. 5Z-7-oxozeaenol also increases hyperthermia induced cleavage of caspase-3 which is one of the central executioners of apoptosis [189].

TAK1 and necroptosis

The process of apoptosis and necrosis are two different and distinct methods of cell death. Apoptosis occurs via two different mechanisms that include the death receptor induced pathway and the mitochondria mediated mechanism. The process of apoptosis is characterized by distinct morphological changes in the cell that include fragmentation of nuclear DNA, membrane blebbing, chromatin condensation and

cell shrinkage [191]. Apart from apoptosis other processes of cell death include necrosis also called as necroptosis, which is also a tightly regulated and programmed form of cell death. Necroptosis is a caspase independent mechanism of cell death and occurs in the cells that are either ATP or mitochondria depleted. Morphological changes that occur during necroptosis include disruption of the plasma membrane, swelling of the cellular organelles, cell lysis and inflammation [192–195]. Necroptosis has recently emerged as a process that contributes in the development of a diverse array of pathological conditions including viral infections, neurodegenerative diseases and ischemic injury. TAK1 s a key molecule involved in the process of necroptosis, however the molecular events that regulate the process are not well characterized. TAK1 is implicated in the regulation of necroptotic signaling via both NFκB-dependent and independent mechanisms [196]. The process of necrosis is considered as the secondary mechanism of cell death prevalent in the cells that cannot appropriately induce caspase-dependent apoptosis [197]. TAK1 inhibition results in inactivation of NFκB, which serves as a cell death checkpoint for both apoptosis and necroptosis. TAK1 is implicated in the NFκB independent cell death mechanisms which involves the formation of two cell death complexes that include the necroptotic cell death complex (RIP1–RIP3-FADD) and the caspase 8-activating complex (RIP1-FADD-capse 8). The formation of both the cell death complexes involves the phosphorylation and activation of RIP1, which is promoted by TAK1 inhibition. Hence, the inhibition of TAK1 promotes both necroptotic and apoptotic cell death. The cell death, both apoptotic and necroptotic, induced by inhibition of TAK1 is inhibited by the ablation of the CYLD, a RIP1 deubiquitinase [196]. In TAK1 deficient cells, Tumor Necrosis Factor-α stimulation results in overriding of receptor interacting protein (RIP1) dependent necroptosis over apoptosis. In TAK1 deficient cells caspase cascade activation and caspase-8 mediated cleavage of RIP1 following TNF-α stimulation is insufficient to block RIP1-dependent formation of necrosome and subsequent necroptosis. TAK1 inhibits the premature dissociation of ubiquitinated-RIP1 in TNFα-stimulated cells and also prevents the formation of TNFα-induced necrosome complex, composed of RIP1, RIP3, FADD, $cFLIP_L$ and caspase-8. This action of TAK1 is independent of its kinase activity. Hence a complex and a surprising regulatory mechanism governs the prevalence of RIP1 dependent necroptosis over apoptosis irrespective of the ongoing active caspase cascade following stimulation of the cell death receptor [197]. TRADD, an adapter protein is a key molecule in the TNF-α induced necroptotic cell death. A novel necroptotic regulatory pathway, the ubiquitin-proteosome pathway, controls necroptosis by regulating the availability of key pro-survival signaling molecules encompassing NFκB, cIAPs and FLIP [196].

Conclusion

A significant body of evidence has contributed in aligning interest in the processes that participate in executing cellular death by virtue of several death programs, the cells are at liberty to exploit. While each of these processes may constitute an independent death program like programmed necrosis, autophagic cell death, apoptosis etc many entities or components that drive these programs seem to overlap and emerge as a common network of pathways with complex crosstalk. In light of a serious relevance of these processes in relating to cancer genesis and their prospect for anti cancer therapy, it has become imperative to highlight and identify their common ties for potential therapeutic application.

TAK1, a MAPK kinase kinase family serine threonine kinase has emerged as a common link to relate many death related programs like apoptosis, autophagy with development and cell survival mechanisms. It ropes in tumor growth factor pathways in crosstalk with cellular stress signaling via JNK, P38 etc. On one hand and engages with energy sensor mechanisms via AMPK and growth regulation processes dominated by mTOR signaling on the other. It has in a way extended its scope as a key player in death and survival dynamics of the cell and has accordingly emerged as a frontline candidate for therapeutic intervention. Although complexity of the cross talking networks continues to remain challenging, it nevertheless provides for a way forward in mitigating the challenge regardless of the magnitude.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest regarding the publication of this paper.

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