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Review

Regulation of TAK–TAB Complex Activation through Ubiquitylation

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Abstract

Transforming growth factor-β (TGF-β) activated kinase 1 (TAK1), also named mitogen-activated protein kinase 7 (MAPK7), forms a pivotal signaling complex with TAK1-binding proteins (TAB1, TAB2, and TAB3), orchestrating critical biological processes, including immune responses, cell growth, apoptosis, and stress responses. Activation of TAK1 by stimuli, such as tumor necrosis factor α (TNFα), interleukin-1β (IL-1β), and Toll-like receptors (TLRs), underscores its central role in cellular signaling. Given the critical role of the TAK1-binding protein (TAK1–TAB) complex in cellular signaling and its impact on various biological processes, this review seeks to understand how ubiquitination thoroughly regulates the TAK1–TAB complex. This understanding is vital for developing targeted therapies for diseases where this signaling pathway is dysregulated. The exploration is significant as it unveils new insights into the activity, stability, and assembly of the complex, underscoring its therapeutic potential in disease modulation.

Keywords: TAK1; TAB1; TAB2; TAB3; ubiquitination

1. Introduction

The mitogen-activated protein kinase (MAPK) cascade is a cornerstone in eukaryotic signal transduction, characterized by a hierarchy of three kinase classes: MAP3K, MAP2K, and MAPK [1]. Among these, transforming growth factor-β (TGF-β) activated kinase 1 (TAK1), also known as MAP3K7, is a critical member of the MAP3K family, which plays a pivotal role in cellular signaling pathways. TAK1 exhibits serine/threonine kinase activity and acts as an upstream regulator, activating the nuclear factor κB (NF-κB) pathway via phosphorylation of IκB kinase (IKK) [1,2]. This activation triggers a cascade of NF-κB-mediated signaling events, underscoring the multifaceted role of TAK1 in biological processes, especially in modulating inflammatory gene expression [3,4].

TAK1-binding proteins (TAB proteins), comprising TAB1, TAB2, and TAB3, are essential and specific binding partners for TAK1. TAB1 binds to the N-terminus of TAK1, while TAB2 and TAB3 associate with the C-terminus of TAK1 under stress-induced signaling [5]. The formation of the TAK1–TAB1–TAB2–TAB3 complex is pivotal for inducing the autophosphorylation and subsequent activation of TAK1 [5]. This activation is essential for the downstream activation of NF-κB and MAPKs, key signaling molecules in inflammatory and immune responses. Decades of research on the TAK–TAB complex have unveiled its central role in cellular biology, physiology, and pathology [5–7].

Ubiquitination, an omnipresent and versatile post-translational modification (PTM), plays a pivotal role in regulating the TAK–TAB complex, affecting its activation, stability, and degradation [8,9]. This review dissects the mechanisms through which ubiquitination governs the TAK–TAB complex, shedding light on its contribution to cellular signaling and potential therapeutic avenues. A deeper understanding of these regulatory mechanisms enhances our knowledge of the TAK–TAB complex and creates new perspectives for targeting these pathways in disease contexts.

2. Composition and Biological Functions of the TAK–TAB Complex

The TAK–TAB complex, central to cellular signaling, comprises the kinase TAK1 and its specific binding partners, TAB1, TAB2, and TAB3 [5]. Initial *in vivo* experiments revealed that global deletion of TAK1 results in early embryonic death due to defects in neural tube formation [10,11]. Similarly, the elimination of TAK1's essential activation partners, TAB1 and TAB2, leads to non-viability because of cardiovascular and liver malformations, respectively [12–14]. Researchers have employed tissue-specific conditional knockouts of *TAK1* to overcome these challenges, gaining deeper insights into its role across different cell types. Such studies have shown that specific knockouts in immune cells disrupt B cell development and the

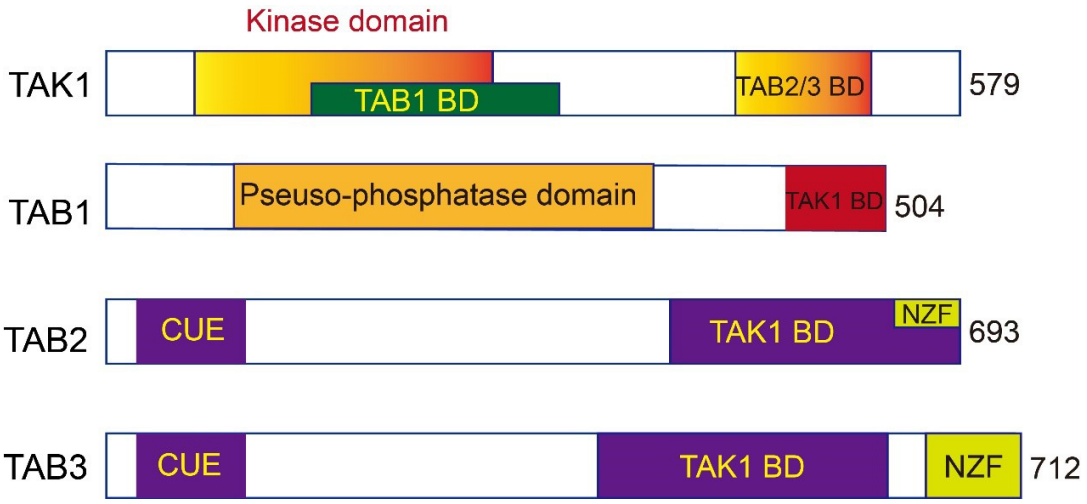

Fig. 1. Schematic illustration of the domain structures of human transforming growth factor-β (TGF-β) activated kinase 1 (TAK1), TAK1-binding proteins (TAB)1, TAB2, and TAB3. TAK1 contains a kinase domain at the N-terminus, followed by a TAB1 binding domain (TAB1 BD) and a TAB2/3 binding domain (TAB2/3 BD). TAB1 is characterized by a pseudo-phosphatase domain and a TAK1 binding domain (TAK1 BD). TAB2 and TAB3 are homologous proteins, and both have a CUE domain at the N-terminus, a TAK1 BD, and an Npl4 zinc-finger (NZF) domain at the C-terminus. CUE, Coupling of Ubiquitin to ER degradation.

immune response to antigens [11], while knockouts in non-immune cells such as the skin, liver, and intestinal cells cause aberrant development and inflammation [15], illustrating the complex and critical nature of TAK1 in both immune and non-immune cellular processes [11,16].

2.1 Structure and Biological Effects of TAK1

TAK1 is a serine/threonine protein kinase featuring an N-terminal domain, a hinge region, and a C-terminal domain [17]. The N-terminal domain of TAK1 contains a conserved kinase domain, which is responsible for its enzymatic activity, phosphorylating specific serine and/or threonine residues on substrate proteins. ATP binds and transfers a phosphate group to the substrate in this kinase domain. The serine-rich and glycine-rich regions within this domain may regulate its kinase activity and play roles in protein–protein interactions (Fig. 1) [12,16].

Research on TAK1 in mice has cast uncertainty on its viability as a therapeutic target. While no TAK1 loss-of-function mutations have been identified in humans, a gain-of-function mutation resulting from a truncated kinase form leads to developmental phenotypes, including craniofacial abnormalities [18]. This highlights the complex role of TAK1 in embryogenesis and development [19]. The discovery underscores the challenges in targeting kinases therapeutically, given the potential for genetic contradictions and the complexity of kinase-mediated signaling pathways, which may involve redundant or compensatory mechanisms [20]. Moreover, the scaffolding roles played by TAK1 further complicate the interpretation of its genetic studies, emphasizing that a nuanced approach is needed in pharmacologically manipulating TAK1 for therapeutic benefits.

The biological actions of TAK1 span various signaling pathways, and its activity is regulated by diverse stimuli, including growth factors, cell adhesion, and inflammatory factors [21]. Upon activation, TAK1 regulates downstream proteins, including adaptor proteins in the NF-κB and MAPK pathways, thereby influencing cell survival, proliferation, differentiation, and death [21]. Studies reveal that embryos lacking TAK1 exhibit developmental abnormalities and embryonic death, while conditional *TAK1* knockout mice manifest a range of physiological defects associated with impaired TAK1 signaling, including reduced inflammation, abnormal cell differentiation, and compromised survival [11,12,22].

Genome-wide association studies (GWAS) have placed TAK1 (MAP3K7) in the spotlight, underscoring its critical role in health and disease, thus marking it as a potential therapeutic target [23–28]. Such studies have connected TAK1 with various diseases, including Crohn's disease, ulcerative colitis, and inflammatory bowel disorder. In particular, GWAS on Japanese rheumatoid arthritis (RA) patients highlighted a significant association of TAK1 with susceptibility to diseases and response to anti-TNF treatments, suggesting its pivotal role in inflammatory disease management [25,29]. The association of TAK1 with diverse conditions, from immune responses to genetic traits affecting biological functions, demonstrates its broad biological impact, emphasizing the need for further research into its mechanisms and therapeutic applications.

Given these diverse roles, TAK1 is considered a key molecular node in signaling networks that determine cell fate and function. Understanding the regulation of TAK1 and its pathways offers potential therapeutic targets for various diseases where its signaling is aberrant.

2.2 Structure and Biological Effects of TAB Proteins

TAK1 binding proteins (TABs) serve as specific binding partners for TAK1 and include TAB1, TAB2, and TAB3. The activation of TAK1 relies on the assembly of these proteins, forming a complex that crucially regulates the kinase activity of TAK1 [5].

TAB1: Characterized by a pseudo-phosphatase domain and a TAK1 binding domain (TAK1 BD) (Fig. 1). The pseudo-phosphatase domain in TAB1 has a similar structure to protein phosphatase 2C (PP2C), despite lacking phosphatase activity. It interacts directly with the N-terminal kinase domain of TAK1 [30]. Disrupting this interaction can result in late-stage pregnancy edema and hemorrhage. *In vitro* experiments have found that TAB1 is indispensable for TAK1 activation through autophosphorylation [5,31].

TAB2 and TAB3: Homologous proteins that share 48% of their amino acid sequences, indicating a significant evolutionary relationship. They feature an N-terminal coupling of ubiquitin to ER degradation (CUE) domain, a C-terminal TAK1 binding domain, and a Npl4 zinc-finger (NZF) domain [14,16] (Fig. 1). The TAK1 binding domain in TAB2 and TAB3 is primarily responsible for binding with TAK1, while the CUE domain binds directly to ubiquitin, linking ubiquitinated proteins to endoplasmic reticulum degradation [32]. The NZF domain is responsible for binding polyubiquitin chains, specifically recognizing the polyubiquitin chains linked by lysine (K)63, crucial for TAK1 activation [33]. Although structurally similar, TAB2 and TAB3 can complement each other in certain functions. *TAB2* gene knockout results in embryonic death in mice, while *TAB3* gene knockout mice can be born normally, suggesting specific roles in regulating TAK1 activity [14,16].

Through their binding domains, TAK1 and TAB1 are associated in unstimulated cells [31]. Upon stimulation, TAB2 and TAB3 bind to the C-terminal region of TAK1 through their respective binding domains, forming the TAK1–TAB1–TAB2/TAB3 complex. The functional assembly of TAK1 with TAB proteins in response to cellular stimuli underscores the complex's versatility in regulating various biological processes. This interaction activates critical signaling pathways and reflects the complex's adaptability to diverse cellular contexts, from immune responses to stress responses [12]. The detailed study of the TAK–TAB complex reveals its fundamental role in cellular signaling and disease mechanisms, presenting opportunities for therapeutic intervention.

3. TAK–TAB Complex-Mediated Signaling

TAK1, a pivotal multifunctional kinase, is a critical upstream regulator in the NF-κB and MAPK signaling pathways. It also functions as a downstream target for numerous cell factors, including tumor necrosis factor α (TNF-α), TGF-β, interleukin-1 (IL-1), Toll-like receptor (TLR) ligands, and various stress stimuli [10,21], activating TAK1 through phosphorylation and initiating classic IκB kinase (IKK) complex-involved NF-κB activation and MAPK signal transduction (Figs. 2,3) [34]. Studies are increasingly exploring how TAK1 interacts with other proteins and pathways, including its regulation through ubiquitination and its potential as a therapeutic target. The value lies in uncovering new therapeutic strategies for diseases where TAK1 signaling is dysregulated, offering insights into cancer, autoimmune disorders, and inflammation [2].

3.1 TNF Receptor (TNFR)-Mediated TAK–TAB Signaling

TNF serves as a central cytokine in inflammatory responses and a common ligand in the NF-κB and MAPK pathways [35,36]. Upon TNF binding to TNF receptor 1 (TNF-R1), a trimeric complex form, which recruits the TNF receptor-associated death domain (TRADD) [37] through the death domain (DD). Subsequently, TRADD recruits TNF receptor-associated factors (TRAF) 2/5 and cellular inhibitors of apoptosis proteins 1/2 (c-IAP1/2), forming the TNF–R1 signaling complex. This complex recruits RIP1, leading to K63-linked polyubiquitination of RIP1. The polyubiquitin chains on RIP1 bind to the C-terminal NZF domain of TAB2/TAB3, promoting the formation of the TAK1/TAB1/TAB2/TAB3 complex and triggering conformational changes for TAK1's autophosphorylation-dependent activation [38]. This activation further activates TAK1, initiating the IKK complex and ultimately activating NF-κB. TRAF2-mediated K63-linked polyubiquitination plays a critical role in TNFR1-induced TAK1 activation.

Recently, GWAS studies have underscored the pivotal role of TNF–TAK1 complex signaling in the pathogenesis of diverse conditions, illuminating the critical function of TAK1 as a therapeutic target. For example, GWAS findings in Asian populations with rheumatoid arthritis (RA) underscore the involvement of MAP3K7 (TAK1) and its activator, TAB1, suggesting a nuanced genetic predisposition [23]. Furthermore, single-nucleotide polymorphisms (SNPs) within the TNF–TAK1 axis have been linked to a heightened risk of inflammatory diseases, including Crohn's disease and ulcerative colitis, implicating genes such as *MAP3K7* and *TNFSF18*, among others [24,26,27]. Despite the advancement of biological therapies targeting TNF, the emergence of resistance highlights the necessity of alternative strategies [39,40]. The advent of selective TAK1 inhibitors represents a promising avenue, with preclinical studies validating the efficacy of blocking TAK1 in RA [41]. This development not only broadens our therapeutic arsenal but also emphasizes that it is imperative for further research to elucidate the intricate role of TAK1 within inflammatory pathways.

3.2 IL-1R and TLR-Mediated TAK–TAB Signaling

IL-1, also known as lymphocyte-activating factor, is mainly produced by monocytes/macrophages and exists in two forms: IL-1α and IL-1β. IL-1R has two types, with

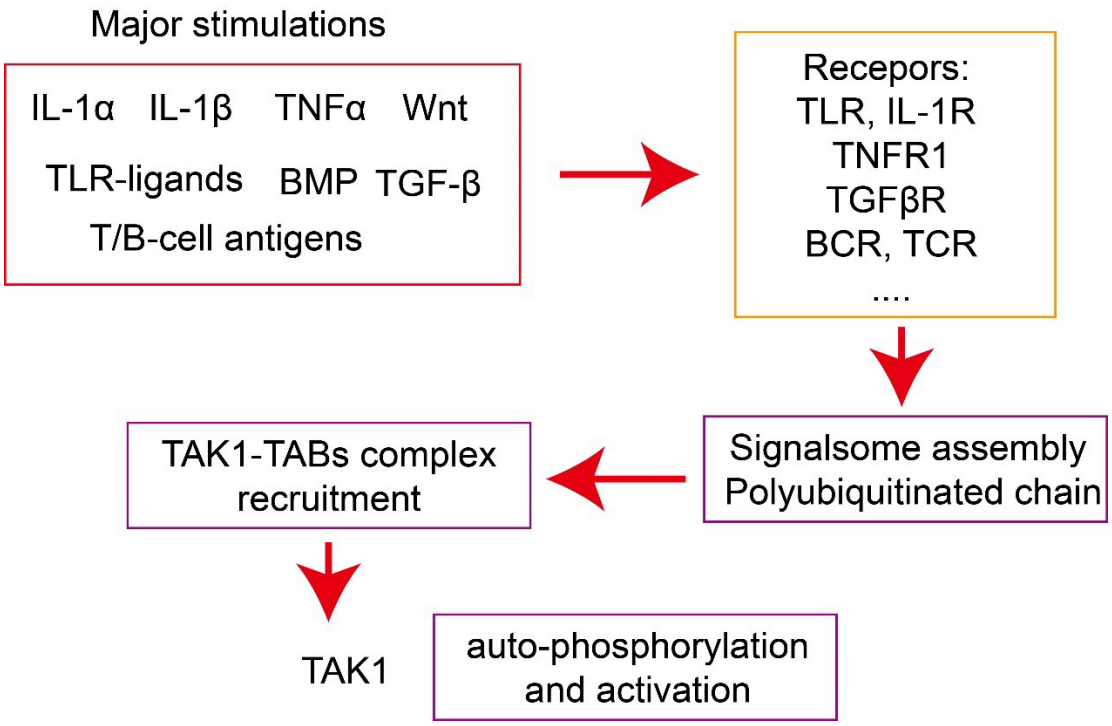

Fig. 2. Activation of TAK1–TAB complex. Major stimulations, including cytokines, such as interleukin (IL)-1α, IL-1β, tumor necrosis factor α (TNF-α), growth factors, such as bone morphogenetic protein (BMP) and TGF-β, and antigenic stimuli from T/B-cells lead to the activation of various receptors such as the Toll-like receptor (TLR), IL-1R, TNF receptor 1 (TNFR1), transforming growth factor (TGF)βR, B-cell receptor (BCR), and T-cell receptor (TCR). Upon receptor stimulation, the signalosome is assembled, forming a polyubiquitinated chain, which subsequently leads to the recruitment of the TAK1–TAB complex. Then, the TAK1 enzyme undergoes autophosphorylation and becomes activated, a critical step in the signal transduction process for inflammatory and immune responses.

IL-1RI being the most abundant. IL-1RI binds to both IL-1α and IL-1β. In the IL-1β signaling pathway, IL-1β induces conformational changes in the extracellular domain of IL-1RI, recruiting the IL-1 receptor accessory protein (IL-1RAcP) to form the IL-1β/IL-1RI/IL-1RAcP trimeric complex. This complex recruits MyD88, initiating a signaling cascade involving IRAK4 and IRAK1 (IL-1 receptor-associated kinases) [42–44]. Phosphorylation of IRAK1 by IRAK4 releases IRAK1 into the cytoplasm, forming a signaling complex with E3 ubiquitin ligase TRAF6, which undergoes oligomerization, leading to the synthesis of K63-linked polyubiquitin chains by E2 enzymes Ubc13 and Uevi1A [45]. These polyubiquitin chains, binding to the highly conserved zinc-finger-NZF domains of TAB2 and TAB3, cause low oligomerization and autophosphorylation of TAK1 at Thr184 and Thr187 [46,47]. Subsequently, TAK1 phosphorylates IKKs and MAPKs, activating NF-κB and AP-1 downstream pathways, contributing to natural immunity and inflammation regulation [48].

Members of the TLR family recognize antigen components of different types of microorganisms and are well-studied pattern recognition receptors (PRRs). Both IL-1R and TLR receptors share Toll/interleukin-1 receptor domains in their intracellular signaling-related structures and, when activated, can bind MyD88 through these Toll/interleukin-1 receptor domains [42,43,49]. MyD88 [44], containing a death domain, then recruits IRAK1/4, TRAF6 and initiates downstream NF-κB pathway activations [48,50].

3.3 Participation of TAK–TAB in TGF-β Signaling

The TGF-β signaling pathway is one of the most crucial signaling pathways, involved in regulating cell growth, proliferation, differentiation and aging, cell death, cell adhesion, migration, extracellular matrix synthesis, and remodeling [22,51]. The TGF-β family signals through the I-type receptor (TβRI) and II-type receptor (TβRII) complex integrity, which is essential for TGF-β signal transduction. TGF-β family ligands form a dimer and bind to TβRII and TβRI on the membrane, inducing the phosphorylation of TβRII by TβRI and activating its kinase activity. Subsequently, TβRI recruits and activates downstream signaling molecules, initiating the canonical Smad and non-Smad signaling pathways [52–55].

Previous research has established TAK1 as a key upstream signaling molecule in the non-Smad signaling pathway induced by TGF-β1. However, the impact of TAK1 on activating the classic Smad signaling pathway remains a subject of debate [56]. Our previous studies have revealed that TAK1 can simultaneously affect the activation of both

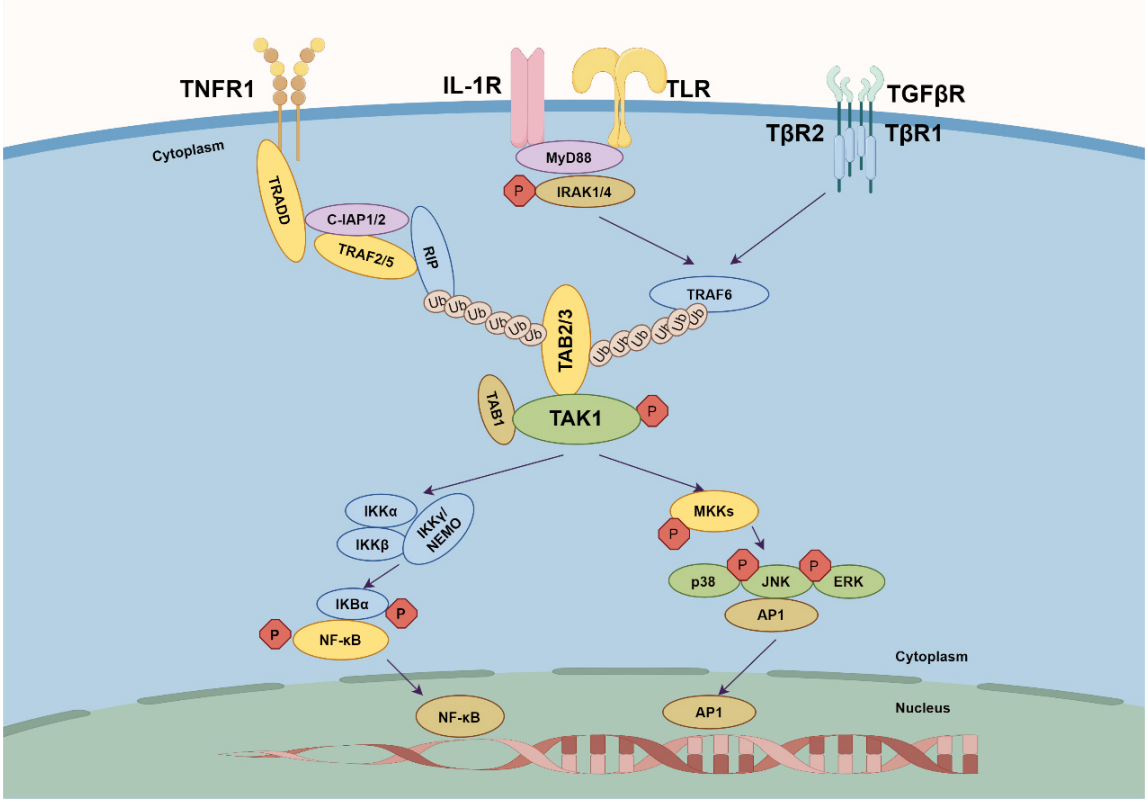

Fig. 3. TAK–TAB complex-mediated signaling. Four key receptors are shown: TNFR1, IL-1R, TLR, and TGFβR, each initiating a cascade of intracellular events. Upon activation, these receptors interact with specific adaptor proteins (such as MyD88 for IL-1R and TLR and TRAF2/5 for TNFR1), leading to the recruitment and activation of the TAK1 complex via TAB2/3. Once activated, TAK1 activates downstream kinases, including p38, JNK, ERK, and NF-κB.

Smad and non-Smad signaling pathways induced by TGF-β1, thereby influencing the pathological changes associated with hypertensive nephropathy [57].

4. Ubiquitination Modification of the TAK1–TAB Complex

Given the crucial role of the TAK1–TAB complex in various signaling pathways responding to diverse immune stimuli, the regulatory cascade mediated by TAK1–TAB has been extensively explored [12]. The TAK1–TAB complex undergoes dynamic post-translational modifications, including phosphorylation, ubiquitination, methylation, acetylation, O-GlcNAcylation, and SUMOylating [16,58–60]. These modifications are not mutually exclusive and can interact with each other, further adding to the complexity of regulating the TAK1–TAB complex.

Given the breadth of this topic, the subsequent discussion will focus on elucidating the role and mechanisms specifically associated with the ubiquitination of the TAK1–TAB complex. This aspect is particularly critical as it affects the degradation and recycling of these proteins and profoundly impacts their function in signaling pathways, such as those leading to NF-κB activation, which in turn regulate immune and inflammatory responses. Understanding these mechanisms is pivotal for potential therapeutic interventions targeting diseases where TAK1–TAB signaling is dysregulated.

4.1 Clinical Significance of Ubiquitination Modification in the TAK1–TAB Complex

In the context of disease, the dysregulation of TAK1/TAB ubiquitination has been implicated in the pathogenesis of autoimmune conditions, tumor growth, and neurodegenerative diseases [8,21,61]. The excessive or prolonged activation of NF-κB signaling due to ubiquitination imbalance can exacerbate these conditions [62,63]. Therefore, understanding and manipulating the ubiquitination process of the TAK1/TAB complex creates new therapeutic avenues. The potential to modulate this pathway offers promising strategies for treating related diseases and conditions. Moreover, alterations in the ubiquitination pattern of these proteins might serve as valuable biomarkers for the early detection, diagnosis, and prognosis of diseases [16]. This aspect of ubiquitination is critical for developing a holistic understanding of the role of the TAK1–TAB complex in health and disease [8,45,60].

Ubiquitination, a pivotal post-translational modification, intricately regulates cellular processes critical for maintaining homeostasis [8,64], including the cell cy-

cle, proliferation, and apoptosis [65]. The ubiquitin–proteasome system (UPS) is crucial for protein degradation, similar to the regulatory roles of kinases [66,67]. Disruptions in ubiquitination pathways can lead to an imbalance in these processes, significantly contributing to many disorders, including cancer, neurodegenerative diseases, and issues related to adaptive and innate immunity [68,69]. Recent studies have underscored the dual role of ubiquitination in either promoting or inhibiting tumor progression, depending on the context and the specific proteins being targeted, while the UPS was also demonstrated as a potent target for anticancer therapy [67,68,70]. Deubiquitinating enzymes (DUBs) have emerged as critical regulators within this context, capable of removing ubiquitin modifications and, thus, reversing the effects on target proteins. Many DUBs have demonstrated tumorigenic roles in multiple cancers, and many inhibitors have been investigated in clinical trials for diverse cancer treatments [70]. Given their central role in modulating the stability and activity of key proteins involved in tumorigenesis, DUBs represent promising targets for therapeutic intervention, offering the potential for developing novel anticancer strategies [70]. However, the FDA has currently only approved a few drugs that target the ubiquitin system [66].

The advancements in ubiquitin biology have led to innovative strategies for modulating the ubiquitination system, with significant implications for therapeutic development [67]. For the past decade, proteasome inhibitors have been utilized in treating multiple myeloma (MM), yet resistance to these inhibitors has emerged, impacting their effectiveness. Bortezomib (Velcade) and carfilzomib (Kyprolis) are FDA-approved proteasome inhibitors effective against multiple myeloma [66]. Techniques such as proteolysis-targeting chimera (PROTAC) molecules [71] and hydrophobicity tags (HyT) [72] have been developed to specifically target and manipulate the degradation of proteins, offering precise approaches to treat diseases caused by dysregulation of the ubiquitination process [68]. Furthermore, the advent of small molecule inhibitors targeting ubiquitination enzymes presents a promising direction in treating conditions such as cancer, highlighting the potential of these molecular interventions in precision medicine [66].

4.2 Ubiquitination

Ubiquitination and phosphorylation are among the most crucial and widely studied post-translational modifications. It is a dynamic and versatile mechanism for controlling various aspects of cellular function [8,9]. Ubiquitin, a small yet pivotal protein in cellular regulation, consists of 76 amino acids and is notable for its seven lysine residues—K6, K11, K27, K29, K33, K48, and K63—plus an N-terminal methionine (M1) that can all serve as attachment points for forming polyubiquitin chains [64,73]. The functions and implications of ubiquitination through K6, K27, K29, and K33 are less well-characterized and represent an area ripe for further research [74,75]. This ubiquitination system is a key regulator of intracellular proteins, influencing as much as 80% of them [70]. The consequences of ubiquitination can vary greatly (Fig. 4).

Proteasomal degradation: Ubiquitin chains, particularly those linked through the K48 residue, often signal the protein to be directed to the 26S proteasome for degradation. This is a key process for removing damaged, misfolded, or unneeded proteins, thereby regulating protein levels and quality control within the cell [73]. **Altering substrate activity:** Ubiquitination can also change the functional state of proteins, either activating or inhibiting their enzymatic activity, altering their cellular location, or affecting their ability to interact with other molecules [64]. **Mediating protein–protein interactions:** Ubiquitin chains can serve as a platform for assembling protein complexes, which is critical in various signaling pathways. For example, K63-linked ubiquitin chains are often involved in processes such as DNA repair, NF-κB signaling, and the regulation of cellular trafficking [73]. Given its versatility, ubiquitination is a fundamental regulatory process essential for maintaining cellular homeostasis and responding to stress.

Ubiquitination encompasses non-proteolytic roles such as receptor internalization, multiprotein complex assembly, intracellular trafficking, and key signaling pathways, including those governing inflammation, autophagy, DNA repair, and enzymatic regulation [76–78]. Deregulation can trigger oncogenic pathways, disrupt cellular metabolism, and lead to inadequate protein complex formation critical for inflammation response or DNA repair, resulting in the accumulation of misfolded proteins, causing diseases such as neurodegeneration or misdirecting proteins away from their functional locations within the cell [8,79].

Ubiquitination is a multistep process typically involving the coordinated action of three ubiquitination enzymes: ubiquitin-activating enzyme (E1), ubiquitin-conjugating enzyme (E2), and ubiquitin-protein ligase (E3) [64]. Initially, the E1 forms a high-energy thioester bond between the carboxyl group of the C-terminal lysine residue of ubiquitin and the thiol group of its own cysteine residue, utilizing ATP-provided energy. Subsequently, the activated ubiquitin is transferred onto the cysteine residue of the E2. Finally, a member of the highly conserved ubiquitin-protein ligase family, E3, recognizes specific target proteins to be ubiquitinated and catalyzes the transfer of ubiquitin molecules from E2 to the lysine residue of the target protein (Fig. 5) [64]. Really interesting new gene (RING) finger [RNF] proteins containing RING domains act as E3 ubiquitin ligases that mediate the covalent linkage of ubiquitin to target proteins [9]. Depending on the ubiquitin chain's topology, ubiquitination can lead to proteasomal degradation or mediate protein–protein interactions, influencing various cellular processes [64]. Understanding these

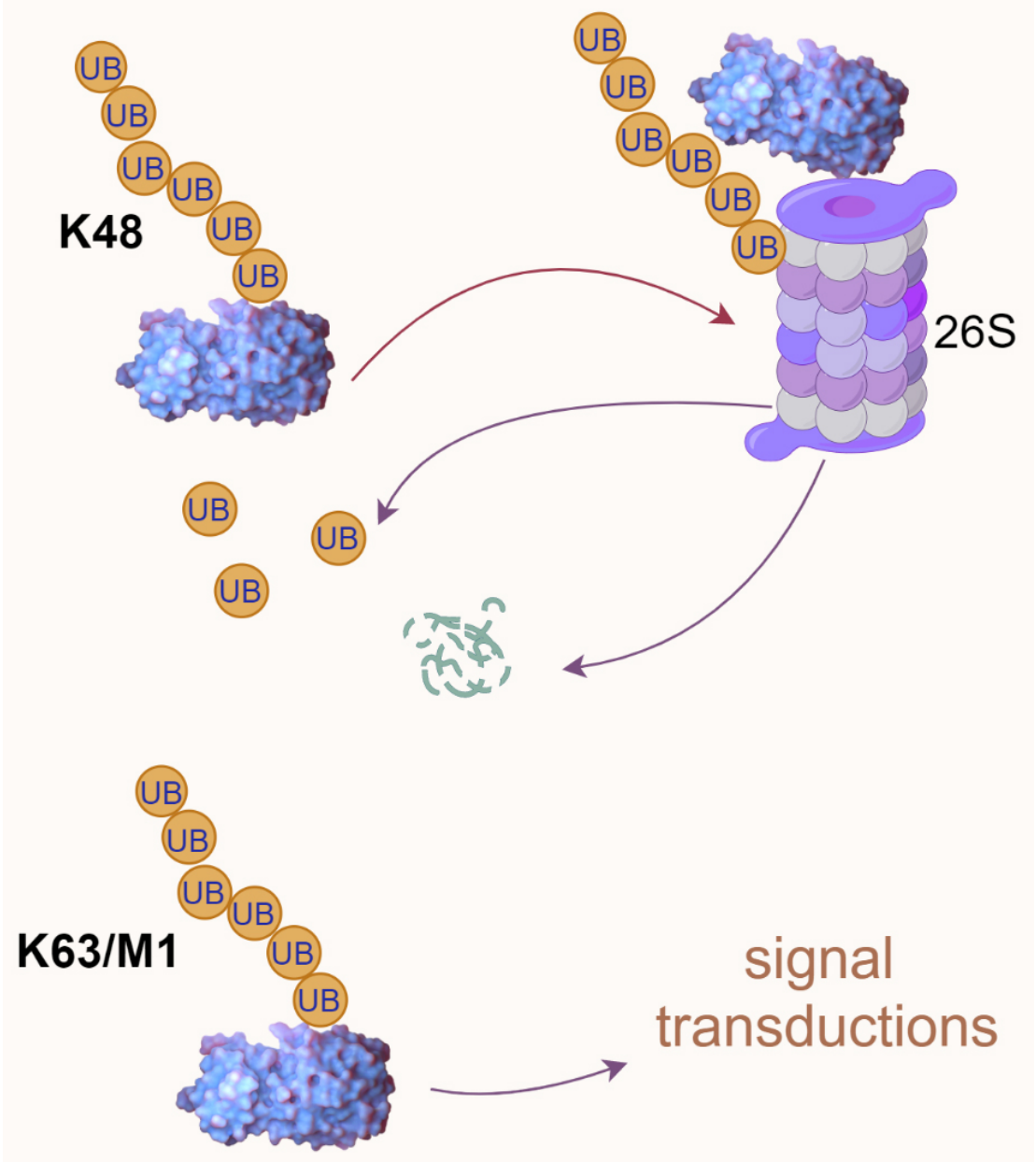

Fig. 4. Ubiquitin-mediated proteasomal degradation and signal transduction. K48-linked polyubiquitination is typically associated with proteasomal degradation, as illustrated by a polyubiquitinated protein directed to the 26S proteasome. In contrast, K63/M1-linked polyubiquitination is often involved in signal transduction processes. UB, ubiquitin.

processes provides insights into the molecular mechanisms of diseases involving the TAK1–TAB complex and offers new opportunities for drug development.

4.3 Ubiquitination Regulation of the TAK1 Complex and Its Mediated Biological Functions

4.3.1 Ubiquitination Modification of TAK1

TAK1 undergoes sophisticated regulation via different ubiquitin chain types, including K63-linked and K48-linked ubiquitination, each dictating unique biological outcomes [16]. E3 ubiquitin ligases, notably TRAF6 and TRAF2 [80–84], are pivotal in this regulation, intricately influencing TAK1's cellular role. K63-linked polyubiquitination, identified at lysine residues K34, K158, K209, and K562, is crucial for TAK1 activation, with TRAF6 and TRAF2 mediation highlighting a complex regulatory network. A study by Fan *et al.* [81,85] revealed that the activation of TAK1 via NF-κB and MAPK pathways might transcend polyubiquitination at traditional sites, such as K34 and K209, suggesting the existence of alternative regulatory mechanisms that merit further exploration.

Recent investigations have expanded our understanding of TAK1 activation, revealing that its function may not solely depend on ubiquitination at known sites, suggesting

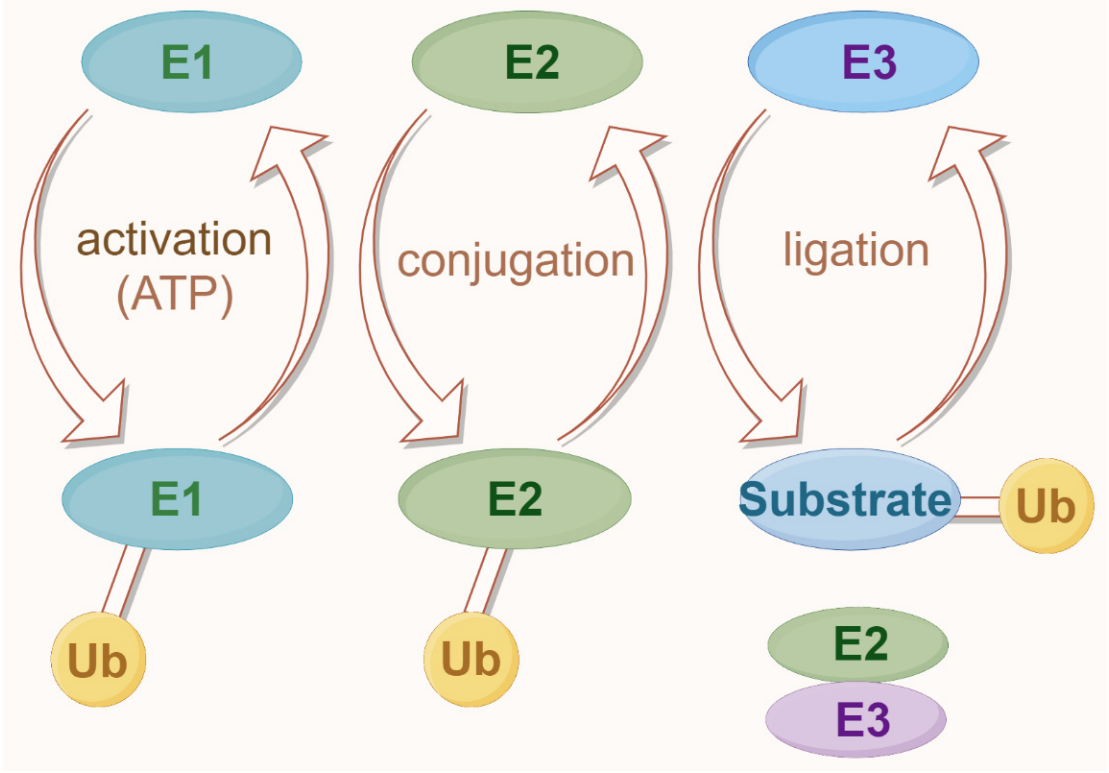

Fig. 5. The ubiquitin modification system. Ubiquitination begins with the activation of ubiquitin (Ub) by the E1 enzyme, which is ATP-dependent. Activated ubiquitin is then transferred to the E2 conjugating enzyme. In the final step, the E3 ligase enzyme facilitates the attachment of ubiquitin to the substrate protein, completing the ubiquitination process.

a labyrinth of regulatory pathways yet to be explored. The tripartite motif-containing (TRIM) protein family [9], notably **TRIM8** [86,87] and **TRIM27** [88], emerges as significant modulators within the TAK1/NF-κB signaling pathway, showcasing the multifaceted nature of TAK1 regulation through diverse ubiquitination patterns. This complexity is further exemplified by additional E3 ligases such as **Sef-S** [89] and the carboxyl terminus of HSC70-interacting protein (**CHIP**) [90], each contributing to the nuanced modulation of TAK1's function through specific ubiquitin linkages. The role of phosphorylated TAK1 (p-TAK1) in cellular homeostasis underscores the importance of targeted ubiquitination in maintaining kinase activity balance, with **TRIM16** [91], **ITCH** [92], and **FBXW2** [93] facilitating critical regulatory steps through K48-linked ubiquitination, leading to proteasomal degradation or functional modulation of TAK1. In addition to the conventional seven types of polyubiquitin chains, **TRIM56** has been reported recently to interact with TAK1 and enhance its M1-linked ubiquitination modification, thereby increasing the transcription of NF-κB downstream genes [94]. Our preliminary research introduces a novel dimension to TAK1 regulation, identifying the unique role of **TRIM31** in promoting K48-linked ubiquitination and subsequent degradation of TAK1. This process serves as a vital checkpoint in TAK1-mediated signaling, particularly in the context of TGF-β1-induced renal inflammation and fibrosis, underscoring the potential of ubiquitination dynamics as therapeutic targets [57].

These investigations suggest that TAK1 activation is intricately modulated beyond known ubiquitination sites, hinting at a broader spectrum of regulatory pathways awaiting discovery. The involvement of the TRIM protein family, among other E3 ligases, in modulating TAK1 through diverse ubiquitination patterns underscores the multifaceted nature of its regulation. This complexity is crucial for maintaining cellular homeostasis and highlights the potential for targeted therapeutic interventions in diseases associated with TAK1 pathway dysregulation (Table 1, Ref. [57,61,80–84,86–104]).

4.3.2 Ubiquitination Modification of TAB1

TAB1, a critical regulator of TAK1 activity through direct interaction, is subject to a complex regulatory network via polyubiquitination and other post-translational modifications, including phosphorylation and O-GlcNAcylation [105,106]. This multilayered modification landscape underscores the pivotal role of TAB1 in cellular signaling dynamics. Notably, both K63 and K48-linked ubiquitination have been observed on TAB1 [61,95,96], highlighting its versatile regulatory capabilities.

K63-linked ubiquitination of TAB1, particularly at lysine residues Lys294, Lys319, Lys335, and Lys350, is me-

diated by various E3 ligases, including the E3 ubiquitin ligase activity of the mitogen-activated protein kinase kinase 1 (MEKK1) the plant homeodomain (**PHD**) [61]. This modification is crucial for enhancing TAK1 aggregation and its kinase activity, significantly influencing embryonic stem cell differentiation and tumorigenesis. Intriguingly, recent discoveries, such as the work by Yuan *et al.* [95], have illuminated the role of **RNF207** in activating the TAK1–JNK1/2 signaling pathway through K63-linked ubiquitination of TAB1, linking it to the exacerbation of stress-induced pathological cardiac hypertrophy.

TAB1 can also undergo K48-linked ubiquitination, although the specific modification sites remain unclear. Immune regulation is essential for maintaining skin integrity. Research by Theivanthiran *et al.* [96] suggests that **ITCH** can catalyze K48-linked polyubiquitination on TAB1, inhibiting the activation of p38α and providing new insights into preventing inflammatory skin diseases.

In addition to K63 and K48-linked ubiquitination, other types of ubiquitination also play crucial roles in TAB1's functions. In a study by Zhao *et al.* [97], **TRIM26** was found to catalyze K11-linked polyubiquitination on TAB1 at positions Lys294, Lys319, and Lys335, enhancing the activation of TAK1 and subsequent NF-κB and MAPK signaling. On the other hand, E3 ligase **RNF114**, by promoting ubiquitination and degradation of TAB1, indirectly affects NF-κB activation during maternal-to-zygote transition (MZT), although the specific type and sites of ubiquitination on TAB1 still need further clarification [98].

This enriched understanding of TAB1's ubiquitination broadens our perspective on its regulatory functions and underscores the potential for targeting these modifications in therapeutic strategies, especially in contexts of cellular stress responses and disease pathogenesis.

4.3.3 Ubiquitination Modification of TAB2 and TAB3 and their Corresponding Biological Functions

TAB2 and TAB3 recognize and bind to ubiquitinated substrates and undergo self-ubiquitination, thereby finely tuning the intensity and duration of signal transduction [12,107]. Human TAB2 and TAB3 feature two conserved ubiquitin-binding domains: the N-terminal CUE and C-terminal NZF domains. The CUE domain, a universal ubiquitin-binding structure, includes the phenylalanine–proline (Phe–Pro or FP) motif crucial for ubiquitin-binding [33,108]. Although the precise role of the CUE domain in TAB2 and TAB3 remains unclear, studies suggest that the absence of this domain partially reduces the ability of TAB2 and TAB3 to activate NF-κB. However, it does not completely inhibit this process, possibly due to the collaborative action of the CUE and NZF domains in providing specificity for recognizing K63 ubiquitin chains (required for TAK1 activation) [62]. TAB2 and TAB3 lacking the CUE domain may fail to distinguish between different types of ubiquitin chains, potentially impacting their binding to K63 polyubiquitin chains and subsequently reducing their activation capability [62]. The interplay between these domains underscores a sophisticated mechanism for TAB2 and TAB3 to discern and bind various ubiquitin linkages, significantly affecting their roles in NF-κB activation and cellular signaling pathways.

The ubiquitin-modified TAB2 and TAB3 primarily serve two functions. First, the NZF domain within TAB2 and TAB3 facilitates the binding to K63-linked polyubiquitin chains on partner proteins such as RIP and TRAF6 [33]. This interaction is crucial for activating TAK1, leading to the regulation of downstream signaling cascades that govern immune and inflammatory responses, cellular autophagy, and apoptotic processes [62]. Conversely, ubiquitination can signal the degradation of TAB2 and TAB3, thus attenuating inflammatory responses. Theoretically, both proteins can be targeted for degradation within the cell through their NZF domains, which can also bind to K48-linked polyubiquitin chains—the classic marker for proteasomal degradation [33,109]. However, current research suggests that TAB2 and TAB3 have a higher binding affinity for K63 chains over K48 chains [62,107]. Notably, TAB3 exhibits a significantly lower affinity for K48 chains than TAB2, indicating that TAB2 may be more prone to degradation via the K48 ubiquitination–proteasome pathway. This differential affinity for ubiquitin chains suggests distinct regulatory mechanisms for TAB2 and TAB3, influencing their stability and function in cellular signaling pathways [62,107].

Their modification significantly influences the functionality of TAB2 and TAB3 through various E3 ubiquitin ligases, such as TRAF6 and members of the TRIM protein family. Upon stimulation with cytokines such as TNFα and IL-1β, TAB2 and TAB3 are ubiquitinated by **TRAF6** [62], which is critical for assembling the TAK1–TAB signaling complex. TRIM proteins, including **TRIM5**α [110], **TRIM22** [111], **TRIM27** [88], **TRIM30**α [112], and **TRIM38** [113,114], have been identified as mediators that target TAB2 and TAB3 for lysosome-dependent degradation. However, the specific interaction sites and the roles of these TRIM proteins in ubiquitinating TAB2 and TAB3 are not fully elucidated. TRIM38 [113,114], in particular, has been shown to inhibit NF-κB activation induced by TNFα and IL-1β by mediating the lysosomal degradation of TAB2 and TAB3, resulting in decreased activity of TAK1. A study by Shi *et al.* [112] on the regulation of TAB2 by TRIM proteins highlighted that TRIM30α can bind and promote the degradation of both TAB2 and TAB3. The inhibition of this degradation process by lysosome inhibitors, rather than proteasome inhibitors, suggests that the actions of TRIM27 and TRIM30α occur primarily through lysosomal degradation pathways [88]. However, the precise mechanisms behind this remain to be fully understood.

Other E3 ligases, such as **RNF4**, have also been implicated in the lysosomal degradation of TAB2 or TAB3.

Moreover, selective autophagy, particularly mediated by the autophagy receptor NBR1, is another pathway through which TAB3 may be degraded [115]. Qiu's [111] research has presented that **TRIM22** can interact with TAB2 independently of its RING domain and lead to the degradation of TAB2 via the proteasome pathway. Nevertheless, the necessity of TAB2 ubiquitination for TRIM-mediated degradation is yet to be conclusively determined, and further experimental research is needed to validate the specific modifications of TAB2.

K48-linked protein ubiquitination modification directs degradation through the proteasome pathway [64]. It has been demonstrated that **TRIM29** catalyzes substrate ubiquitination through its B-box domain rather than the typical RING domain. Dou's [99] study found that TRIM29 in NK cells can bind to TAB2, mediating ubiquitination and proteasome degradation of Lys48-linked TAB2, thereby inhibiting the production of IFH-γ in activated NK cells. The E3 ubiquitin ligase RBCC protein interacts with protein kinase C1 (RBCK1) and has ubiquitin ligase activity. Research indicates that RBCK1 negatively regulates TAK1 signal transduction through K48-linked polyubiquitination and degradation of TAB2 and TAB3 at C673 and C692 separately [100]. **TRIM45**, also named **RNF99**, has been clarified as a key regulator of neuroinflammation after cerebral ischemia-reperfusion (IR) injury in research by Xia [101]. The study indicates that TRIM45 directly binds to TAB2 through its RING domain, promoting K63-linked polyubiquitination of TAB2 but not K48-linked polyubiquitination [101]. Interestingly, in our study concerning inflammatory organ damage, **RNF99** was discovered to selectively regulate K48-linked ubiquitination at Lys611 on TAB2 [102]. This mediation leads to proteasomal degradation of TAB2, inhibiting signal transduction of TAK1–TAB2–NF-κB/MAPKs, ultimately playing a protective role in inflammatory organ damage [102]. This specificity reflects the complex nature of cellular functioning and the importance of understanding these proteins within the precise context of each tissue and cell type to develop targeted and effective therapeutic interventions.

A recent study has indicated a potential link between **TRIM23** and TAB2 ubiquitination in macrophages and the alleviation of kidney symptoms in diabetic mice. However, further verification is required to determine whether TRIM23 directly mediates the ubiquitination of TAB2. Nonetheless, the direct involvement of TRIM23 in the ubiquitination process of TAB2 remains to be conclusively established [103].

Sun's [104] study on the ubiquitination of TAB3 reveals that the autocrine motility factor receptor (**AMFR**), an E3 ubiquitin ligase anchored to the endoplasmic reticulum (ER) in an ER-dependent and loop-dependent manner, directly interacts with TAB3, inducing K27-linked polyubiquitination of TAB3 at Lys649 and promoting TAK1 activation.

Emerging research points to a diverse landscape of ubiquitination-induced regulatory mechanisms for TAB2 and TAB3, implicating various E3 ligases in their modification. This diversity underscores the complexity of cellular signaling regulation and the potential of targeting these pathways for therapeutic intervention. Further investigations into the specific roles and interaction sites of E3 ligases will undoubtedly deepen our understanding of TAB2 and TAB3 regulation, paving the way for novel insights into cellular dynamics and disease pathogenesis.

4.4 Deubiquitination Modification of TAK1–TAB

The activation of NF-κB via the TAK1–TAB complex is intricately controlled through various regulatory mechanisms, including the critical process of deubiquitination, which counteracts ubiquitination [60,116–118]. Deubiquitination involves the removal of ubiquitin moieties from proteins by specific deubiquitinating enzymes (DUBs) [66]. The interplay between ubiquitination and deubiquitination is a dynamic and finely balanced process central to maintaining cellular protein homeostasis. This selective deubiquitination can affect protein–protein interactions, influencing the formation and disassembly of protein complexes essential for accurate signal transduction and cellular responses [119]. The disruption of these processes is often implicated in cancer pathogenesis, underlining the importance of these mechanisms in controlling cell growth and proliferation [120].

Several DUBs, each with distinct roles, are instrumental in regulating the TAK1–TAB complex. By selectively removing ubiquitin chains from these proteins, these enzymes can alter the activity, stability, and interaction of TAK1 and TABs, thereby fine-tuning the signaling pathways they are involved in [118,121–123]. This targeted deubiquitylation is crucial for precisely controlling signaling events that govern cellular processes such as inflammation, cell survival, and proliferation, with implications for both normal physiology and disease states, including cancer [63].

4.4.1 Deubiquitination Modification of TAK1

Enzymes such as USP4, USP18, USP19, and CYLD [118,121–123], along with members of the TRIM family, such as TRIM44 [124] and TRIM15 [125], are known to modulate the functions of the TAK1 and TAB proteins through their specific deubiquitinating activities (Table 2, Ref. [92,116–118,121–128]).

USP4: Inhibits the activation of NF-κB induced by TNF by removing K63-linked polyubiquitin chains on TAK1 at K158 [63]. The interaction protein P38IP also facilitates TAK1's USP4-dependent deubiquitylation [116, 121,126]. **USP8:** Directly interacts with TAK1 and removes K63-linked ubiquitin chains, inhibiting the activation of NF-κB, thus playing a regulatory role in IHR-induced inflammation [127]. **USP18:** Induced by interfer-

Table 1. Ubiquitination of TAK1 and TABs.

Protein	Catalyzed by	Site	PTM	Reference
TAK1	TRAF6	K34, K158, K562	K63 Ub	[80–84]
	TRAF2	K158	K63 Ub	[82]
	TRIM8	K158	K63 Ub	[86,87]
	Sef-S	K209	K63 Ub	[89]
	CHIP		K63 Ub	[90]
	ITCH	K72	K48 Ub	[88,92]
	TRIM31	K72	K48 Ub	[57]
	TRIM16	K282, 547	K48 Ub	[91]
	FBXW2		K48 Ub	[93]
	TRIM56		M1 Ub	[94]
TAB1	PHD	K294, K319, K335, K350	K63 Ub	[61]
	RNF207		K63 Ub	[95]
	ITCH	S452, S453, S456, S457	K48 Ub	[96]
	TRIM26	K294, K319 K335	K11 Ub	[97]
	RNF114		Ub	[98]
TAB2	TRIM29		K48 Ub	[99]
	RBCK1	C673	K48 Ub	[100]
	RNF99	K611	K48 Ub, K63 Ub	[101,102]
	TRIM23		Ub	[103]
TAB3	AMFR	K649	K27 Ub	[104]
	RBCK1	C692	K48 Ub	[100]

PTM, post-translational modification; K, lysine; C, cysteine; Ub, ubquitination.

ons in immune cells, USP18 negatively regulates TAK1–TAB activity by removing K63-linked ubiquitination from the TAK1–TAB complex [117,118]. **USP19:** In response to TAFα or IL-1β, USP19 interacts with TAK1, selectively removing K63- and K27-linked polyubiquitin chains. This disrupts TAK1 kinase activity, impacts the formation of the TAK1–TAB complex, and ultimately influences NF-κB signaling [123]. **CYLD:** A deubiquitinase with specificity for K63-linked linear ubiquitin chains, CYLD critically regulates NF-κB activation. It acts on various components of NF-κB signaling, including TAK1, by specifically removing K63-linked ubiquitin chains, preventing the spontaneous activation of TAK1, and negatively regulating NF-κB activation associated with cell survival and cancer [92]. **TRIM family (TRIM44 and TRIM15):** Most members of the TRIM family possess ubiquitin ligase activity, although TRIM44 and TRIM15 are the exceptions. TRIM44, with a zinc-finger ubiquitin protease domain (ZF-UBP) at its N-terminus instead of a RING domain, maintains TAK1 stability by inhibiting K48-linked ubiquitination-mediated degradation [124]. TRIM15, through interaction with TAK1, negatively regulates the TNFα signaling pathway by inhibiting K63-linked ubiquitination [125].

The exploration of DUBs such as USP4, USP18, USP19, and CYLD, in conjunction with TRIM family members such as TRIM44 and TRIM15, underscores their pivotal roles in modulating the function and regulation of the TAK1–TAB signaling complex [60,116–118]. These enzymes orchestrate a delicate balance within cellular signaling pathways, particularly those implicated in inflammation and immune responses. By engaging in specific deubiquitinating actions, these DUBs and TRIM proteins contribute to a sophisticated regulatory network that maintains cellular homeostasis and modulates the body's response to various stresses and pathological states [8].

4.4.2 Deubiquitination Modification of TABs

The stability of TAB2 and TAB3 is vital for cellular homeostasis, regulated by a balance between their degradation and stabilization through lysosomal and proteasomal pathways [5–7,16]. This equilibrium is influenced by ubiquitination, marking the proteins for degradation or protection, crucial for their roles in inflammation, immunity, and apoptosis [129]. Understanding how this balance is maintained can reveal insights into cellular signaling and offer new targets for treating diseases related to pathway dysregulation. Further research into these mechanisms is essential for advancing our knowledge of cellular processes and developing therapeutic interventions.

In a notable advancement, Zhou *et al.* [122] identified that **USP15**, a deubiquitinating enzyme, is critical in regulating TAB2 by cleaving K48-linked ubiquitin chains. This action by USP15 curtails the degradation of TAB2, which would typically occur via lysosomal pathways, thereby en-

hancing the stability of TAB2 and contributing to the subsequent NF-κB signaling activation. In the case of TAB3, USP15 has been found to obstruct the NBR1-mediated selective autophagic degradation of TAB3, an effect that interestingly occurs independent of its deubiquitinating activity. This discovery opens new avenues for understanding the intricate regulation of cellular processes and suggests potential therapeutic targets for diseases involving NF-κB dysregulation.

Furthermore, ubiquitin-specific protease 14 (**USP14**) [128], which is known to be a significant player in proteasomal degradation, has been implicated in the development and progression of various cancers. Research indicates that USP14 can interact with TRAF6 without altering its ubiquitination status. Yet, it can promote the deubiquitination of TAB2, a known substrate of TRAF6. This action attenuates NF-κB activity, suggesting a nuanced regulatory role where USP14 modulates the NF-κB pathway indirectly through its effect on TAB2 rather than directly through TRAF6. These findings underscore the complex interplay of ubiquitination and deubiquitination in cellular signaling and the potential of these enzymes as targets for therapeutic intervention [119].

Deubiquitinating enzymes play a crucial role in the NF-κB signaling pathway, fine-tuning cellular responses by removing ubiquitin from specific lysine residues on TAK1 and TAB proteins [66,119]. This selective deubiquitination process is vital for controlling NF-κB pathway activation, impacting the signaling intensity, duration, and protein turnover, thus maintaining cellular balance and adapting to environmental changes. Targeting these enzymes offers a promising approach to modulating NF-κB signaling in diseases such as chronic inflammation, autoimmune disorders, and cancer, suggesting their potential as therapeutic targets [119,120]. Further research into these enzymes could lead to novel treatments, enhancing our understanding of cellular regulation and paving the way for precision medicine.

Table 2. Deubiquitination of TAK1 and TABs.

Protein	Catalyzed by	Site	PTM	Reference
TAK1	USP4	K158	K63 de-Ub	[116,121,126]
	USP8		K63 de-Ub	[127]
	CYLD	K209	K63 de-Ub	[92]
	USP18		K63 de-Ub	[117,118]
	USP19		K63 de-Ub K27 de-Ub	[123]
	TRIM15		K63 de-Ub	[125]
	TRIM44		K48 de-Ub	[124]
TAB2	USP15		K48 de-Ub	[122]
	USP14		de-Ub	[128]

PTM, post-translational modification; K, lysine; C, cysteine; Ub, ubquitination; de-Ub, Deubiquitination.

5. Conclusions and Perspectives

Within the MAP3K family, TAK1 is crucial in orchestrating signaling pathways for inflammatory responses, interacting closely with TAB proteins to significantly influence the NF-κB and MAPK pathways. This interaction, pivotal for cellular signal transduction, involves intricate ubiquitination and deubiquitination processes that affect a broad spectrum of physiological and pathological processes. Despite progress in identifying key enzymes such as E3 ubiquitin ligases and DUBs, the detailed mechanisms of their regulation, especially how they respond to specific stimuli across different cell types, remain to be fully understood.

The dysregulation of the ubiquitination of the TAK–TAB complex is linked to the onset of numerous diseases, from chronic inflammation to cancer, highlighting the importance of understanding these mechanisms for developing targeted therapies. Enhancing our knowledge in this area could lead to groundbreaking drug discoveries. Research challenges include precisely controlling the activity of the TAK1–TAB complex and avoiding potential side effects of interventions. Thus, a deeper investigation into the functional mechanisms of TAK1 is vital for crafting more effective treatments. Furthermore, this regulation through ubiquitination underscores the broader significance of post-translational modifications in cellular signaling balance, promising advancements in therapeutic innovations through continued exploration.

The progress in bioinformatics, mass spectrometry, and high-throughput screening technologies has made developing specific E3 inhibitors for the TAK1–TAB complex more achievable. Techniques such as phage display have been utilized to create ubiquitin variants that can specifically inhibit E3 ligases and DUBs [130]. Moreover, computer-aided drug design has led to innovative therapeutic strategies that can disrupt E3 ligase-substrate interactions [66]. The advent of degrader technologies such as PROTACs, HyTs, and selective estrogen receptor degraders (SERDs) opens new avenues for drug development in targeting the TAK1–TAB complex, potentially leading to significant clinical advancements.

Author Contributions

MZ, YZ and CZ contributed to the conception and design of the work. JZ, LC, LJL, WQQ, WY, CYK and RQR collected the literature and information to write the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work. All authors contributed to editorial changes in the manuscript. And all authors read and approved the final version of the manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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