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Review Article

An Update on the Role and Mechanisms of TPL2 in Pathogenic Microbial Infection

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Abstract

Tumor progression locus 2 (TPL2) is a serine-threonine kinase that is essential for the activation of the MAPK/MEK1/2-ERK1/2 signaling pathway. It is also a major host immunity regulator and plays a critical role in host immune responses. In order to further elucidate the effects of TPL2 in pathogenic microbial infections, the effects and underlying mechanisms of TPL2 in the pathogenic infections, such as that of the virus, bacteria, and parasites were reviewed. Here, we provide an overview of the multifaceted functions of TPL2 and the molecular mechanisms in pathogenic microbial infections.

Keywords: TPL2; Pathogenic microbial infection; Regulation mechanism; Research advances

Abbreviations

TPL2: Tumor Progression Locus 2; KD: The Kinase Domain; PRR: Pattern Recognition Receptor; PAMPs: Pathogen-Associated Molecular Patterns; IKKβ: IK Kinase β; Ub: Polyubiquitination; M.Tb: *Mycobacterium Tuberculosis*; LPS: Lipopolysaccharides; CDI: *Clostridium Difficile*; DSS: Dextran Sulfate Sodium; GBS: Group B Streptococcus; DC: Dendritic Cells.

TPL2 Gene

Tumor progression locus 2 (TPL2) is a serine-threonine kinase that belongs to the protein kinase MAP3K family. Miyoshi et al. initially identified Cot (Cancer Osaka Thyroid) as an oncogene in the early 1990s from the SHOK hamster embryonic cell line that was transfected with the DNA from human thyroid carcinoma cell lines [1]. The rat homolog of Cot was named as TPL2. The two translation initiation sites of TPL2 (M1 and M30) give rise to equal molar levels of the 58-kDa (p58) and 52-kDa (p52) proteins. TPL2 is a 467-Amino Acid (AA) cytoplasmic protein, comprising of three parts: the amino-terminus (N-terminus), the kinase domain (138AA–388AA), and the carboxy-terminus (C-terminus), and the C-terminal degradation determinant (degron, 435aa-457aa) is very important for the protein stability of TPL2 (Figure 1). However, removal of the C-terminal domain appears to activate transforming potential of TPL2 by two mechanisms. First, C-terminal truncation increases the specific kinase activity of TPL2, and it has been suggested that the C-terminal may modulate TPL2 catalytic activity by folding back onto the kinase domain [3-4]. Second, C-terminal truncation removes a degron sequence (amino acids 435-457) that promotes the proteolysis of TPL-2 by the proteasome [4]. The C-terminal truncated sequence "degron" (435-457) has elevated kinase-specific activities, suggesting that this region could inhibit the kinase activities of TPL2 [5].

The regulation of protein kinase activity is generally achieved by reversible phosphorylation modification [6]. In contrast to the activation of inflammatory signals, TPL2 also undergoes phosphorylation, which is separated by polyacrylamide gel electrophoresis (SDS-PAGE). There will be a mobility shift due to phosphorylation modification. Multiple laboratories use mass spectrometry to identify a series of phosphorylation sites when TPL2 is activated: Ser62, Ser125, Thr80, Ser141, Thr290 Ser400, Ser413, Ser443, et al., only the phosphorylation of Ser62, Thr290, and Ser400 has been proved to be necessary for TPL2 kinase activity [7-9], and the phosphorylation function of other sites needs further study.

Activation of TPL2

Pattern Recognition Receptors (PRRs), such as TLRs, PLRs, NLRs, and CLRs, specifically recognize the molecular structures of pathogenic microorganisms to induce the signaling cascades, and therefore, activate the expression of specific cytokines and chemokines. Under stable conditions, TPL2 is associated with NF-κB1p105 and ABIN2; however, it has no activities on the downstream MEK (ERK kinase). The target molecules of Pathogen-Associated Molecular Patterns (PAMPs) could be recognized by TLRs, which in turn, stimulate the intracellular signal transduction. The activation of IK kinase β (IKKβ) induced by PAMPs could mediate the phosphorylation of NF-κB1p105, as well as the consequent polyubiquitination (Ub) and proteasomal degradation, followed by the release of TPL2 from the complex (Figure 2). The TPL2 that dissociated from the complex is sensitive to MEK and could be proteolyzed by the proteasome, which could limit the duration of MEK activation. Then, MEK phosphorylates ERK, and in turn, activates various transcription factors, which could result in positive or negative regulatory effects on the transcription of pro-inflammatory genes [5]. Therefore, the IKK complex directly regulates the activation of MAP kinases, such as NF-κB1 and ERK, in innate immune responses via NF-κB1p105 [10].

Roles and Mechanisms of TPL2 in Pathogen Infection

Roles and mechanisms of TPL2 in bacterial infection

Mycobacterium Tuberculosis (M.tb) [11-13] and *Listeria monocytogenes* [14-16] are intracellular pathogens, while macrophages have been considered as the major type of cell infection. The activation of ERK1/2 in macrophages after TLRs stimulating depends on TPL2 [17]. In addition, the dysregulation of cytokines in *Tpl2*$^{-/-}$

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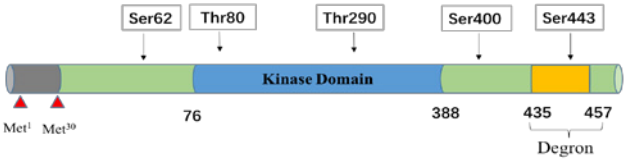

Figure 1: TPL2 structure and phosphorylation sites. The open reading frame of TPL2 is 467 amino acids in length and consists of three parts: the N-terminal domain, the kinase domain and the C-terminal domain. There are two translation initiation sites for M1 and M30 on the mRNA, encoding equimolar levels of 58-kDa (p58) and 52-kDa (p52) isoforms. C-terminal truncation, however, results in a protein with increased kinase-specific activity, suggesting that this region may inhibit TPL2 kinase activity.

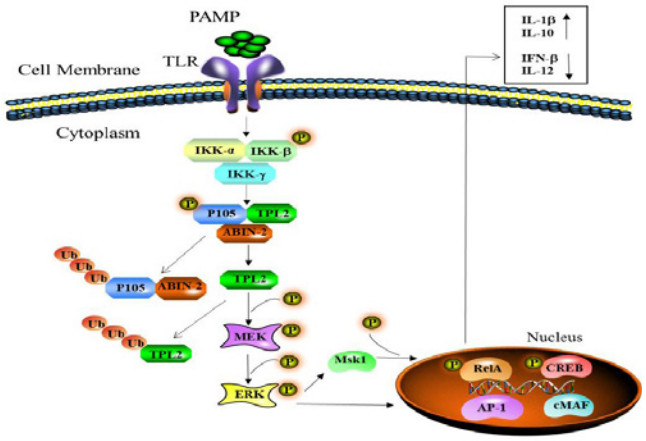

Figure 2: Schematic illustration of the activation and functioning of TPL2. Under stable conditions, TPL2 binds to NF-κB1p105 and ABIN2 but does not affect the downstream substrate MEK (ERK kinase). The pathogen-associated molecules of PAMPs are recognized by TLRs, which stimulate the intracellular signal transduction. The induction of IKK-induced p105 proteolysis leads to the release of NF-κB1 that translocates to the cell nucleus to regulate the target genes. After the release of p105, TPL2 directly phosphorylates MEK, and thus, activates the downstream ERK/MAP kinase signaling.

mice increases the susceptibility to M.tb and *Listeria monocytogenes* infections. Previous studies demonstrated that TPL2-ERK1/2 signaling pathway could negatively regulate the production of type I IFN, and thus, plays a critical role in controlling the intracellular bacterial infection (Figure 3). The infection of macrophages with M.tb activates the TPL2-ERK1/2 pathway to induce the production of the transcription factors. The level of TNF-α is upregulated after the transcription of TPL2 [18, 19]. According to the previous findings, M.tb could regulate the miRNA expression in host cells. For instance, the miR-144 expression is downregulated in macrophages infected with M.tb. The miR-144 could directly bind to the 3'-UTR of TPL2 and exert negative regulatory effects. In addition, inhibiting of miR-144 or overexpression of TPL2 could induce the phosphorylation of ERK1/2, and therefore, activate the ERK signaling pathway [20]. TPL2-defective mice are easier to suffer intracellular bacterial infection. The increased susceptibility of *Tpl2*$^{-/-}$ mice could be partially attributed to the defects of innate immune responses [21]. Therefore, the infection of *Tpl2*$^{-/-}$ macrophages with *Listeria monocytogenes* could reduce the production of TNFs and IL-1β; however, the cells are susceptible to the pathological changes induced by bacteria [22]. A recent study

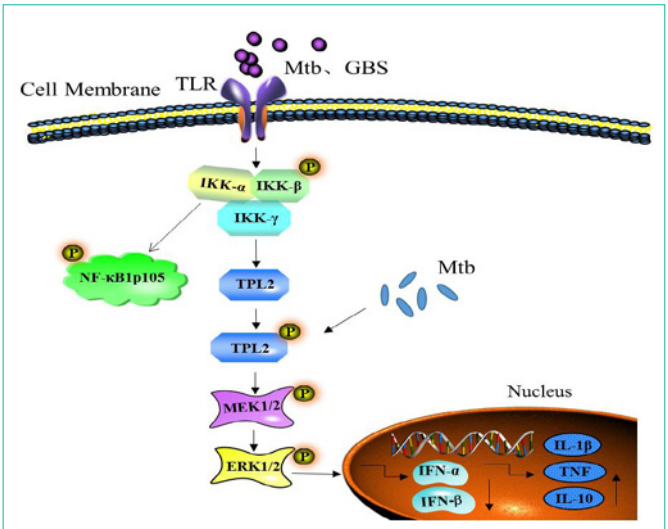

Figure 3: TPL2-ERK1/2 signaling pathway negatively regulates the production of type I IFN. The TLRs and other PRRs expressed by the innate immune cells activate the signaling pathways, and thus, activate various NF-κB1, MAPKs, and IFNs regulators, as well as inflammatory factors, which corporately promote the induction of the pro-inflammatory cytokines, such as TNF, IL-10, and type I IFN. The dysregulation of the production of cytokines in *Tpl2*$^{-/-}$ cells increases the susceptibility to M.tb and *Listeria monocytogenes in vivo*, which depends on the type I IFN signal transduction.

showed that compared to the wild-type mice, *Tpl2*$^{-/-}$ CD4 T cells in mixed bone marrow chimeras were less likely to differentiate into Th1 and Th17 cells expressing IL-17A and IFN-γ, respectively. This defect was confirmed to be intrinsic to T cells. However, *Tpl2*$^{-/-}$ CD4 T cells transferred into *Rag*$^{-/-}$ mice were as protective as wild-type CD4 T cells in preventing bacterial dissemination and mortality, suggesting critical T cell-extrinsic functions for TPL2 in protection against C. *rodentium infection* [23]. Strikingly, the elevated type I IFN and IL-10 levels increased the susceptibility of *Tpl2*$^{-/-}$ mice to intracellular bacterial infection. After stimulating the TLRs of macrophages, the expression of FOS, a transcription factor at the downstream of a TPL2-ERK1/2 signaling pathway, regulated several cytokines, including IL-12, IL-10, and type I IFN [24-26], suggesting that the TPL2-ERK1/2 pathway at the downstream of PRRs effects the responses against M.tb (Table 1). Monocytes secrete the inflammatory cytokines and generate Reactive Oxygen Species (ROS) to promote bacterial clearing and function as the first defensive line of the innate immune system. TPL2 ablation impairs the neutrophil TNFs secretion in response to Lipopolysaccharide (LPS) stimulation, superoxide generation in response to the chemotactic peptide fMLP, and killing of the extracellular bacterium such as *Citrobacter rodentium*. These findings suggested that TPL2 regulates multiple neutrophil antimicrobial pathways, including oxidative burst and the secretion of inflammatory cytokines (Table 1). Thus, it can be inferred that *Tpl2*$^{-/-}$ mice are unable to induce the development and function of immune T regulatory cells to against extracellular bacteria in the early stage of infection [27]. In addition, TPL2 deficiency could increase the susceptibility of *Staphylococcus xylosus* infection in *Rag1*$^{-/-}$ mice, which confirms the importance of TPL2 in the innate immune cells [28]. *Clostridium Difficile* Infection (CDI) is an enteric pathogen that generates spores and toxins. The major virulent factors of CDI are two types of secretory protein toxins: Tcd A and Tcd B.

Table 1: Role of TPL2 signaling in pathogenic microbial infection.

Pathogenic Microbial	Host Mediator	Signal Pathway	Effect On Pathogen Replication	References
Mycobacterium Tuberculosis	miR-144	MAPK−ERK1/2	inhibit	[20]
Citrobacter Rodentium	MEK/ERK	MAPK	inhibit	[23]
Clostridium Difficile	ERK/JNK	MAPK-ERK/JNK	promote	[29]
Intracellular Bacterial	ERK1/2	MAPK −ERK1/2	inhibit	[21]
Listeria	NF-κB	MAPK/NF-κB	inhibit	[22]
Staphylococcus	Superoxide	NADPH	inhibit	[28]
Group B Streptococcal Disease	MyD88	MAPK	inhibit	[37]
Toxoplasma Gondii	Jak2/Stat4/ERK	MAPK	inhibit	[40,41]
Leishmania	ERK/JNK/ NF-κB	MAPK	promote	[45]
Vesicular Stomatitis Virus	IRF3/7	RIG-I	inhibit	[2,51]
Rabies Virus	NF-κB/MAPK	RIG-I	inhibit	[53]
Influenza Virus	Akt/ERK	RIG-I	inhibit	[62]
Gamma-Herpesvirus	AP-1	MAPK	promote	[52]

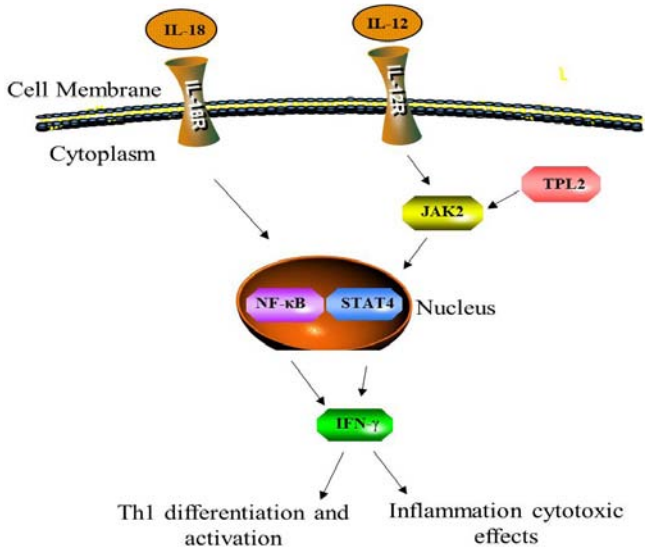

Figure 4: TPL2 kinase regulates the production of IFNs. *Tpl2*$^{-/-}$ leads to impaired IFNs production, which confirmed the inherent defects of T cells. The CD4^{+} T cells separated from *Tpl2*$^{-/-}$ mice show T-bet induction and unstable Stat4 upregulation, which is associated with the defects in activating the TCR-dependent extracellular signaling regulatory kinase. These findings suggested that TPL2 functions as a T cell accessory regulator and plays a critical role in regulating the Th1 responses.

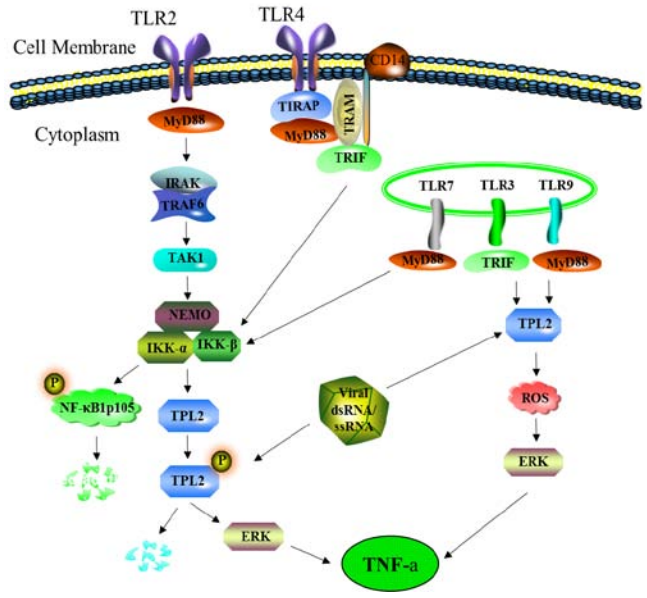

Figure 5: Model of TPL2-ERK activation in the process of TLR signal transduction. The stimulation of TLR2, 4, and 7 immediately activate the IKKβ-TPL2-ERK inflammatory pathway. In addition to TLR adaptor protein, the activation of this pathway by TLR4 requires the co-receptor CD14. Thus, activating the IKKβ to phosphorylate NF-κB1 and TPL2 leads to the release the active TPL2, which phosphorylates ERK before proteasomal degradation. ERK signaling promotes the processing and secretion of TNF-α. TLR3 and 9 could not induce the phosphorylation of TPL2 to induce the degradation or early ERK activation. Conversely, TLR3 and 9 induce delayed ERK phosphorylation via the autocrine signaling of ROS in a TPL2-dependent manner. Therefore, in comparison with other TLRs, TLR3 and 9 could induce the delayed secretion of innate TNF-α.

Previous studies reported that the concentrations of TNF-α, IL-6, and IL-1β are significantly increased in patients infected with CDI [29]. The predominant inflammatory activities of TPL2 depend on the activation of Mitogen-Activated Protein Kinases (MAPKs) and the upregulated production of TNF-α and IL-1β in macrophages and dendritic cells in response to LPS. Furthermore, TPL2 is activated *in vivo* and *in vitro* in response to CDI or *Clostridium difficile* toxin. The inhibition or knockout of TPL2 in mice (*Tpl2*$^{-/-}$ mice) significantly ameliorated the inflammatory manifestations, which further confirms the pro-inflammatory effects of TPL2 during inflammation [30]. In addition, using TPL2 kinase inhibitor for intraperitoneal therapy improves the colitis induced by Dextran Sulfate Sodium (DSS) in mice [31]. These findings demonstrated that TPL2 kinase could be targeted for the treatment of the diseases caused by the elevated levels of TNF-α and IL-1β, thereby suggesting that TPL2 inhibition is a potentially effective treatment method for CDI. TPL2 mutation downregulates the production of type I IFN and increases the susceptibility to Group B Streptococcus (GBS). The mice lacking the type I IFN signal manifest impaired immune

responses against the infection GBS infection and that from various bacteria [32] but enhancing the ability against *Listeria monocytogenes* [33]. In addition, TPL2 is an essential factor for controlling the GBS infection. MAP3K8^{Sluggish} mutant and MAP3K8 knockout animals have high phenotypic similarities, which are manifested as reduced ERK activation [34]. In addition to impairing the production of type I interferons, TPL2 knockout mice also showed a profound impairment of TNF-α production by TPL2-deficient mice in response to TLR signaling and suggest that this may be the major cause for GBS susceptibility. TPL2-deficient mice have significantly reduced levels of IFN-γ (type II IFN) in response to CpG stimulation. TNF-α and IFN-γ play interconnected roles in the host response to GBS. TNF-α released from microbe-stimulated macrophages has been shown to be important for IFN-γ production, and TNF-α and IFN-γ together activate macrophage killing of intracellular bacteria [35,36]. Although the IFN-γ level increased significantly in GBS-infected animals, the impaired IFN-γ production from specific immune cells in a relatively early stage of bacterial infection might increase the GBS susceptibility of TPL2-deficient mice [37].

Roles and mechanisms of TPL2 in parasitic infection

TPL2 has critical innate immunity in the regulation of signaling transductions in the TNF-α, TLRs, and G-protein-coupled receptors pathways. Previous studies have demonstrated that TPL2 mediated the production of IL-12 from T cells, which in turn, is essential for the production of IFN-γ. The stimulation of *Tpl2*$^{-/-}$ CD4^{+} T cells *in vitro* shows an impaired induction of IFN-γ production as well as the low rate of differentiation towards Th1 phenotype. MyD88 is critical for the clearing of Leishmania. Previous studies have reported that MyD88-deficient mice are susceptible to Leishmania infection than control mice [38,39]. These studies have also shown that the lipophosphoglycan, a major parasite molecule, activates the innate immune signaling pathways via TLR2. Additionally, in response to the infection by *Toxoplasma gondii* parasite that induces Th1, TPL2-deficient mice resulted in higher pathogen load associated with decreased systemic IFN-γ production, thereby defining TPL2 as a positive regulator of Th1 responses both *in vitro* and *in vivo*. Therefore, the reduced levels of two factors, T-bet and Stat4, in TPL2-deficient T cells is essential for the differentiation of Th1 cells [40]. Furthermore, TPL2 knockout mice showed decreased IFN-γ production and consequently, increased susceptibility to *Toxoplasma gondii* infection (Figure 4). Surprisingly, the immune response of *Tpl2*$^{-/-}$ mice to intracellular *Toxoplasma gondii* is impaired, which is attributed to the T cells autonomous defects instead of altered innate immune responses [41]. Such responses are related to the pathology of the host defending the pathogen *Toxoplasma gondii*, in which the IFN induction is impaired, and the pathogen load is increased [42]. Cot/*Tpl2*$^{-/-}$ mice showed Th1-skewed antigen-specific immune responses after immunization and Leishmania major infection *in vivo* (Table 1), suggesting that Cot/TPL2 is also a critical negative regulator of Th1-type adaptive immunity. Bacterial DNA rich in the dinucleotide CG (CpG-DNA) activated ERK in a Cot/TPL2 -independent manner. Peritoneal macrophages and bone marrow-derived DCs from Cot/*Tpl2*$^{-/-}$ mice produced significantly more IL-12 in response to CpG-DNA than those from WT mice. Immunization of Cot/*Tpl2*$^{-/-}$ mice with OVA and CFA led to effective proliferation of antigen-specific T cells and increased IFN-γ production. Since Ig class, switching is regulated by cytokines from T cells [43, 44]. These findings are consistent with high IL-12 production and suggest that systemic responses to exogenous antigen are polarized toward Th1 type in Cot/*Tpl2*$^{-/-}$ mice. It inhibits the IL-12 production from accessory cells to achieve such regulation; in addition, it might be a potential target molecule in CpG-DNA-guided vaccination [45]. Firstly, the present study defined TPL2 as a novel IL-12-inducible gene. Stat4 is critical for the host defense and immunoregulation. Currently, several Stat4-dependent genes have been identified [46]. Secondly, TPL2 kinase exerts non-redundant functions in T cells *in vivo*, which in turn, function as the inducible positive regulator of IFN-γ. The *in vitro* polarization of juvenile CD4^{+} T cells from *Tpl2*$^{-/-}$ mice towards the Th1 phenotype was impaired. IL-4 production is a hallmark of the Th2 lineage that defends against helminths and boosts humoral immunity [47], In this setting, continued neutralization of Th2 response (in the presence of neutralizing IL-4 antibody) also could not reverse the Th1/IFN-γ deficiency *in vitro*, suggesting that the impairment of IFN-γ in *Tpl2*$^{-/-}$CD4^{+} T cells could not be simply reversed by enhancing the Th2 response.

Mechanically, TPL2 appeared to exert the effects by affecting the levels of T-bet and Stat4 proteins in activated T cells. The Stat4 expression was declined in the initial TCR-dependent phase. A recent study showed that TPL2 was essential for the stimulation of ERK and MEK on TCR [48]. In addition to the effects in TCR signal transduction, TPL2 might also participate in the T cell co-stimulation pathways. Kane et al. [49] reported that TPL2 binds to protein kinase B (Akt) and then is phosphorylated [50]. In addition, the study demonstrated that the overexpression of Akt could mimic the co-stimulation of IFN-γ inducing the expression of CD28 in T cells. If TPL2 contributed to the co-stimulation signals of CD28, the TPL2 deficiency could impair the co-stimulation of CD28, and therefore, affect the production of IFN-γ. Compared to the wild-type mice, the parasite load was elevated in the *Tpl2*$^{-/-}$ mice that survived the parasite infections (Table 1). These findings suggested that TPL2 is essential for the production of IFN-γ in CD4^{+} T cells.

Roles and mechanisms of TPL2 in viral infection

Signals from TLRs 3 and 9 did not initiate early activation of IKKβ-TPL2-ERK pathway; instead, a delayed NADPH-oxidase dependent ERK phosphorylation and TNF-α secretion were induced via autocrine ROS signaling. Surprisingly, TPL2 is a major regulator of ROS production during TLRs signaling [2]. Due to the defective induction of IL-1β in *Tpl2*$^{-/-}$ macrophages, ROS is vital for the production of IL-1β in response to LPS. In addition to the ROS-mediated ERK phosphorylation in the TLR3 and TLR9 signal transduction, the studies have also confirmed that TPL2 is the critical regulator for ROS production in TLR signal transduction (Figure 5). The immediate activation of TPL2 and ERK during TLR7 signaling also suggested that TPL2 is likely to play a preferential role in host defense against RNA viruses that trigger TLR7. A recent study showed that the replication of Vesicular Stomatitis Virus (VSV) in the embryonic fibroblasts of TPL2 deficient mice was increased [51]. However, MAP3K8/ TPL2 was a positive regulator of murine gammaherpesvirus 68 (MHV-68 or γHV-68) lytic gene expression and replication, and TPL2 enhanced the MHV-68 lytic replication by upregulating the lytic gene expression and promoter activities of viral lytic genes (including RTA and open reading frame 57). Therefore,

TPL2/AP-1 signaling transduction pathway was confirmed to be a positive regulator of MHV-68 lytic replication [52]. These findings confirmed the effects of TPL2 in regulating the viral replication and further underscored the importance of TPL2 in the host immune responses against different pathogens (Table 1). The regulation of downstream NF-κB and MAPK pathways by p105-ABIN2-TPL2 complex was essential for the responses of the host cells to pathogens. For instance, the matrix protein (M) of the field isolates of the rabies virus was previously shown to disturb the signaling induced by RelAp43, an NF-κB protein close to RelA/p65. Interestingly, the M protein interacted not only with RelAp43 but also with TPL2 and ABIN2 (Table 1). Subsequently, the M protein could promote the release of ABIN2 after interaction with the complex and favor the production of RelAp43-p50 NF-κB dimers, and therefore, control the IFNβ, TNF, and CXCL2 expression during the infection of rabies [53]. These findings demonstrated the major effects of RelAp43 and M protein in regulating the NF-κB signaling. However, a prolonged duration is needed to confirm the sequences that M Tha stabilize, release, or block the effects of TPL2 on the MAPK ERK1/2- and MAPK-dependent transcription factors [54]. TPL2/MAP3K8 has been acknowledged as a critical regulator of type I (IFN-α/β) and type II (IFN-γ) IFN and is a major component of the pathways involved in the infection of various viruses, which differentially regulates the induction of IFN-α/β and IFN-λ in a cell type-dependent manner. The Mitogen-Activated Protein (MAP) kinase cascade activates the major intracellular signaling pathways in response to various external stimuli, and the immunity and inflammatory factors during infection. The various intracellular signaling pathways, including NF-κB1, MAP kinase, and IRF, are activated by the infection of the viruses on the receptors, which regulates the induction of anti-viral IFN [55]. Therefore, the MAP is critical in regulating the production of IFN and participating in anti-viral immunity. In MAP kinase, TPL2/MAP3K8 plays a major role in regulating the IFN via promoting the ERK-dependent induction of c-fos (a component of the AP-1 heterodimer transcription factor). Although TPL2 is essential for the production of IFN-α from plasmacytoid dendritic cells (pDC) and IFN-γ from $CD4^+$ T cells, it is also an effective negative regulator for IFN-β production from macrophages and plasmacytoid dendritic cells (pDC) [40,56]. In addition to IFNs, TPL2 also regulates the production of the other major immune factors, including TNF-α, IL-1β, IL-10, IL-12, and COX-2 [18,22,56,57]. Therefore, TPL2 is essential for inducing effective immune responses during infection. Mechanically, TPL2 improves the induction of ISG and virus-specific $CD8^+$ T cells to clear the viruses to exert specific effects, while the deficient $CD8^+$ T cells [58] mediated the reduced ISG expression. This phenomenon increases the susceptibility, as the deficient phenotypes of the anti-viral factors, such as IFITM3, could alter the processes of infection [59]. In addition, the effects of TPL2 on inducing IFN-γ in T cells are associated with TPL2 dependent on the Akt-FOXO1 cascade. Also, the regulation of TPL2 on Akt-FOXO1 signaling in $CD8^+$ T cells demonstrated the anamnestic reaction and anti-viral effects of TPL2 in chronic viral infection [60,61]. TPL2 plays a crucial role in regulating Aktser473 phosphorylation and PI3K/mTOR mediated IFN-λ production. Furthermore, TPL2 could directly transduce the type I IFN signal, leading to the phosphorylation of ERK and STAT1 Ser727, and thus regulating the induction of ISG, which is vital for limiting viral replication. In addition to early innate immune responses, TPL2 could also induce the expansion of specific $CD8^+$ T cells, and thus, promote the clearing of viruses from the infected lungs [62].

IRF7 has been considered as the "major regulator" for the induction of type I IFN in influenza virus infection [63], suggesting that IRF7 plays a major role in inducing the production of IFNα/β. In addition to regulating ISG transcription, TPL2-ERK signaling also regulates the phosphorylation of the translation initiation factor eIF4E, which in turn, participates in the translation of various genes (including ISG15). Therefore, TPL2-ERK pathway regulates the biological effects of IFN at the transcriptional and post-transcriptional levels, while TPL2 not only limits the replication of virus but also regulates the immune responses in the lungs. TPL2 also promotes the host protective immunity during influenza virus infection by integrating the innate and adaptive anti-viral immune responses.

Prospective

Previous studies have reported that TPL2 deficiency could reduce the inflammation in the TNF-dependent inflammatory bowel disease model. The TNF blocker has been demonstrated to be effective in treating various inflammatory diseases, while the TPL2 kinase has been considered as a potential treatment target. In addition, as a potential treatment target for inflammatory diseases including rheumatoid arthritis, TPL2 kinase has attracted increasing attention. However, to date, no pharmaceutical company has endeavored to apply the TPL2 inhibitor in clinical practice. Nevertheless, the selectivity of TPL2 inhibitor could be valuable in assessing the risks and beneficial effects of *in vivo* TPL2 inhibition.

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