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Advancement in TPL2-regulated innate immune response

Ming-Hao Yan, Jun-Hong Hao, Xue-Gang Zhang, Chao-Chao Shen, Da-Jun Zhang, Ke-Shan Zhang*, Hai-Xue Zheng*, Xiang-Tao Liu

State Key Laboratory of Veterinary Etiological Biology, National Foot-and-Mouth Disease Reference Laboratory, Lanzhou Veterinary Research Institute, Chinese Academy of Agriculture Science, Lanzhou, 73004, China

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ABSTRACT

Tumor progression locus 2 (TPL2) is a serine/threonine kinase that belongs to the MAP3K family. The activated TPL2 regulates the innate immune-relevant signaling pathways, such as ERK, JNK, and NF-κB, and the differentiation of immune cells, for example, CD4 + T and NK cells. Therefore, TPL2 plays a critical role in regulating the innate immune response. The present review summarizes the recent advancements in the TPL2-regulated innate immune response.

1. Introduction

The role of innate immunity in disease prevention has attracted increasing attention in recent years. Tumor progression locus 2 (TPL2) is a serine/threonine kinase, also known as MAP3K8 or COT. Without stimulation, TPL2 forms a stable complex with p105 (NF-B1p105) and ABIN2 (A20-binding inhibitor of NF-κB)(Gantke, et al., 2011). Upon stimulation, it regulates the multiple downstream signaling transduction pathways, such as ERK (extracellular signal-regulated kinase), JNK, p38, and NF-κB, via receptors such as TLR, TNFR, and IL1R(Gantke, et al., 2011; Gantke T, 2012; Medzhitov and Horng, 2009). Moreover, TPL2 stimulates macrophages, dendritic cells, neutrophils, and other innate immune cells to produce a variety of chemokines, including IFN-γ and TNF. In addition, TPL2 is vital in regulating CD4 + T cell differentiation into different T helper (Th) cell lineages, thus rendering it essential in innate immune response, inflammation, and carcinogenesis.

2. TPL2 complex and its activation

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). Interestingly, the C-terminus has a degron (435AA–457AA) within the binding region of TPL2 and p105 and plays a critical part in TPL2 protein stability (Fig. 1). 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. Under physiological condition, both isoforms bind to p105 and ABIN2, independently, to form a complex of three proteins, thereby transforming the TPL2 in an inactive state(Cho and Tsichlis, 2005). Although the detectable level of TPL2 in normal cells is associated with p105, a majority of the cells (> 95% macrophages) do not show the binding of intracellular p105 to TPL2(Beinke, et al., 2004). However, the kinase domain (KD) of the protein interacts with p105 death domain (DD)(Yang, et al., 2012), and the TPL2 C-terminus interacts with ABIN2 homeodomain 4 (AHD4), resulting in a stable complex of the three proteins. These interactions block hydrolysis of the NF-κB precursor protein p105, thereby blocking the release of TPL2 from either of the three protein complexes.

Upon lipopolysaccharide (LPS) or tumor necrosis factor alpha (TNF-α) stimulation, p105 is phosphorylated at Ser927/Ser932 residues by IKK, and is then, subjects to proteasome degradation, releasing an active TPL2 that exerts effector functions (Fig. 2). The dissociated p105 is hydrolyzed into p50, which binds to another member of the NF-κB family before translocating into the nucleus to regulate gene transcription (Vougioukalaki, et al., 2011). Among the two isotypes of TPL2, p58 is preferentially released from p105, while the dissociated p58, although active, is unstable and rapidly degraded by the proteasome. Interestingly, TPL2 is predisposed to phosphorylation at multiple residues; however, only Ser62/Thr290/Ser400 residues are essential for activating the TPL2 kinase(Robinson, et al., 2007; Cho, et al., 2005). Furthermore, the phosphorylation at Ser62/Ser400 is autophosphorylation. TPL2 p58 protein is phosphorylated at Thr290, whereas p52 protein cannot be phosphorylated at this residue for release. On the other hand, the interaction between p52 and p58 promotes p58 phosphorylation(Cho and Tsichlis, 2005). IKK is essentially made of IKKα and IKKβ and it is the upstream regulator for TPL2 and favors the phosphorylation of TPL2 at Thr290 residue(Cho, et al., 2005). Thus, it can be concluded that Thr290 residue phosphorylation relies on the

* Corresponding authors at: Lanzhou Veterinary Research Institute, Chinese Academy of Agricultural Sciences, No. 1, Xujiaping, Lanzhou, 730046, PR China.
E-mail addresses: zks009@126.com (K.-S. Zhang), zhenghaixue@caas.cn (H.-X. Zheng).

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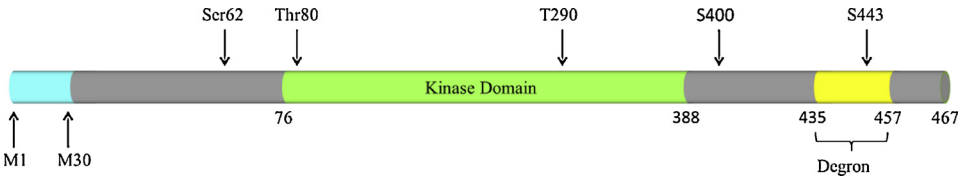

Fig. 1. Illustration of TPL2 primary structure. The open reading frame of TPL2 is 467 amino acids in length and consists of three parts: the N-terminal domain, the kinase domain and the C-terminal domain. The degradation determinant in the C-terminal domain, degron, targets TPL2 for proteasomal degradation. 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. There are also some differences in the function of p58 and p52 with different structures.

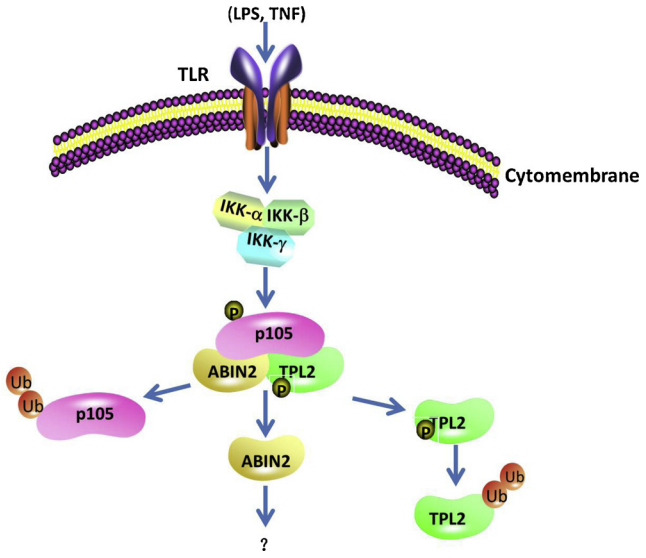

Fig. 2. The process of TPL2 activation. At steady state, TPL2 interacts with p105 and ABIN2 to form a stable trimer complex that maintains TPL2 in an inactive state. Stimulation from TLR (eg, LPS, TNF) results in phosphorylation of IKK-β kinase to stimulate intracellular signal transduction. Activation of IKK-β mediates phosphorylation of p105 and TPL2. TPL2 is phosphorylated at Thr290 by unknown kinases or by autophosphorylation on Ser400 and Ser62 sites, but only phosphorylation of Thr290 is required for the release of TPL2 from p105. P105 subsequently undergoes polyubiquitination (Ub) and proteasomal degradation, releasing TPL2 from the complex. TPL2 released from the trimer complex is active, but its activity is unstable and rapidly degraded by the proteasome.

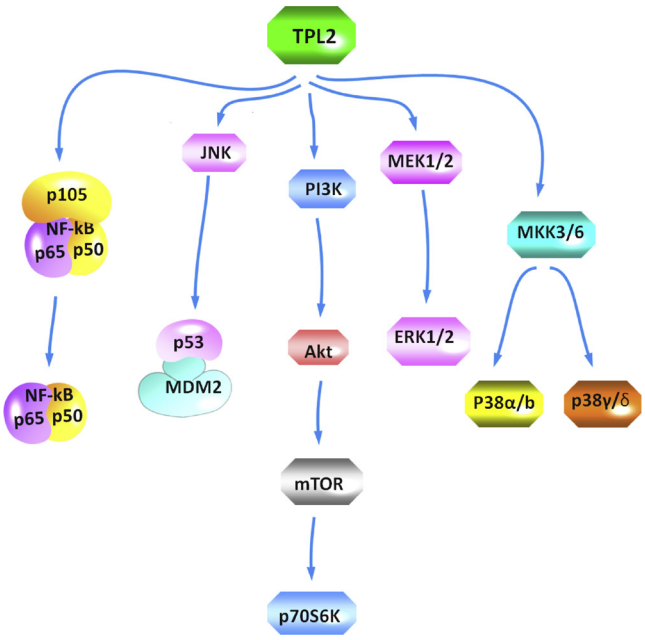

Fig. 3. TPL2 regulates innate immunity signaling pathways. When the pathogen-associated molecular pattern (PAMP) is recognized by various receptors such as TLRs, TNFR and IL1R, TPL2 downstream of the receptor is activated. Activated TPL2 activates the downstream MAPK cell pathway (MEK-ERK, JNK, p38) and is involved in the regulation of NF-κB signaling. Together with the regulation of cell growth, differentiation, environmental stress adaptation, inflammatory response and other important cellular physiological and pathological processes. TPL2 also positively regulates the PI3K-Akt-mTOR-p70 S6k pathway, which inhibits phosphorylation of p38a, JNK, and ERK1/2.

activity IKKα and IKKγ.

3. TPL2 mediates signal transduction and immunoregulation in innate immunity

The key initial step for eliciting an innate immune response is sensing the presence of pathogen-relevant stimulating molecules via TLRs, TNFR, and IL1R receptors. TPL2 is a member of the mitogen-activated protein kinase (MAPK) family, downstream to the receptors, exerting a vital role in MAPK signal transduction. In addition, TPL2 regulates the downstream signaling pathways of MEK-ERK, JNK, p38, and PI3K-Akt-mTOR-p70S6K and the NF-κB signaling pathway via relAP(Krishna and Narang, 2008; Wang and Tournier, 2006) (Fig. 3).

3.1. TPL2 regulates the MEK/ERK signaling pathways

The analysis of primary cells from TPL2 knockout (TPL2-/-) mice demonstrated that the primary function of TPL2 is stimulating the receptors of TLR and TNFR families, which activates ERK during the immune response(Gantke, et al., 2011). TLR differentially activates the TPL2-ERK signaling pathway, and TLR 2/4/7 directly activates the inflammatory axis, positively regulating ERK phosphorylation and early-phase TNF secretion. In addition to these adapter proteins, MyD88-coupled TLR4 specifically requires the accessory molecule CD14 and tyrosine kinase Syk to regulate the activation of IKK-TPL2-ERK signaling pathway. On the other hand, TLR3/9-emanating signals do not elicit an early-phase activation of IKK-TPL2-ERK signaling pathway, rather induce a delayed and indirect phosphorylation of ERK via reactive oxygen species (ROS) autocrine signal transduction, which in turn, causes delayed secretion of innate TNF-α(Kuriakose, et al., 2014). The activation of a TPL2-MEK-ERK signaling pathway in macrophages regulates not only the chemokine production but also the cell response to TNF, IL-1, CD154, and CD40 ligand (CD40 L)(Eliopoulos, et al., 2003; Das, et al., 2005; Banerjee, et al., 2006; Stafford, et al., 2006). TPL2 negatively regulates the LPS-stimulated IFN-β production in macrophages via activated ERK pathways(Yang, et al., 2011). IL-10 is an effective suppressor for TLR-induced expression of multiple genes, including IFN-β and CXCL9. Compared to wild-type cells, p50/p105-/- macrophages exhibit a reduced level of IL-10, thereby raising the IFN-β content(Moore, et al., 2001). Based on these findings, it can be speculated that TPL2 plays a universal role in inflammatory signal transduction, and hence, could be a promising target for anti-inflammation drugs.

TNF is a critical element in inflammatory diseases and is a result of TLRs-elicited multiple signal transduction(Janssens and Beyaert, 2003). Previous studies reported that TACE (TNF converting enzyme), a protease cutting pre-TNF to generate the secretory TNF, in LPS-stimulated

macrophages was phosphorylated at Thr735 by ERK1/2. The activation of the TPL2-MEK1/2-ERK1/2 signaling pathway is essential for TNF production in LPS-stimulated macrophages, and the suppression of ERK1/2 activation diminishes the LPS-induced pre-TNF production. Furthermore, the inhibition of ERK1/2 activation, transiently reduces the mRNA level of pre-TNF(Rousseau, et al., 2008), indicating a crucial role of ERK1/2 in regulating TNF secretion and pre-TNF maturation. Since TPL2 is the sole serine/threonine kinase involved in ERK1/2 activation, it is indispensable for the production of secretory TNF post-stimulation. Thus, it can be hypothesized that TPL2-MKK1/2-ERK1/2 pathway regulates TNF via governing the assembly of a protein complex through pre-TNF breakage, thereby increasing the expression of TNF on the cell surface and not via endocytosis or secretion pathway.

3.2. TPL2 regulates the JNK signaling pathway

p53 pathway monitors the cellular stress signals, and it can impede the survival of cells with unrepairable genetic impair, thereby restraining the tumor development. p53 is the primary tumor suppressor with a critical role in tumor inhibition via cell apoptosis(Levine and Oren, 2009). TPL2 antagonizes the oncogene-induced cell transformation and survival via cJun N-terminal kinase (JNK) downstream of the p53 pathway. TPL2 is essential for the optimal p53 response to genotoxic stress.

A recent study delineated TPL2 as a novel Thr199 NPM kinase. Nucleophosmin (NPM, B23) kinase is a DNA damage response gene, which is primarily localized in the nucleolus and translocates into the nucleus when cells are exposed to DNA damaging agents(Latonen and Laiho, 2005). A portion of TPL2 in the nucleolus is associated with NPM by phosphorylation at Thr199, followed by ubiquitination and degradation. When the cells are exposed to DNA damaging agents (such as ultraviolet rays, UVC), pNPM is dephosphorylated by PP1β phosphatase, succeeded by translocation to the nucleoplasm before binding to HDM2 (MDM2) to form a complex. The interaction between NPM and HDM2 separates HDM2 from p53, thereby inhibiting HDM2-mediated degradation and protecting p53(Kanellis, et al., 2015; Gkirtzimanaki, et al., 2013). A decreased expression of TPL2 resulted in reduced pNPM, which led to less dephosphorylation of pNPM induced by UVC, causing a deficiency in NPM translocation to the nucleoplasm. This phenomenon resulted in HDM2-controlled p53 and impaired p53 accumulation; thus, cell apoptosis is diminished, and malignant transformation accelerated. These findings demonstrated that TPL2 is a positive regulator of the p53 pathway.

Experimental data have proved the role of TPL2 in lung cancer. After exposing TPL2-/- and wild-type mice to ethyl carbamate, the TPL2-/- mice, not the wild-type mice, had pulmonary adenoma in 4 months. Thus, it can be postulated that TPL2 exerts an inhibitory effect on tumors. Further experiments demonstrated that TPL2 knockout impairs JNK and the downstream p53 pathways, resulting in cell apoptosis and accelerating malignant transformation[54], thereby proves the role of TPL2 as a tumor suppressor in lung cancer. It plays a double-edged role in cancer with elevated activity in a variety of human cancers, including breast cancer, colon cancer, thymoma, and lymphoma(Ceci, et al., 1997; Salmeron, et al., 1996; Tsatsanis and Spandidos, 2000; Eliopoulos, et al., 2002). The upregulated expression of TPL2 in various types of tumors indicates its association with carcinogenesis and cancer development. Thus, the key roles of TPL2 in cancer make it a promising target for anti-cancer therapy.

3.3. TPL2 regulates a p38MAPK signaling pathway

TPL2 activates p38 by directly phosphorylating the upstream target MAP2K. The p38MAPK family comprises of high conserved p38α, p38β, p38γ, and p38δ(Cuenda and Rousseau, 2007). Previous studies have already identified the negative feedback loop executed by p38α on TAK1 via TAB1 phosphorylation. A recent study proposed a novel positive feedback loop: TPL2 stimulates p38γ/δ activity via MKK3/6 that further stabilizes the TPL2 activity(Menon and Gaestel, 2016). p38γ and p38δ regulate the stability of TPL2 and ABIN2 proteins via phosphorylation and interaction with the TPL2/ABIN2/p105 complex. p38γ/δ knockout impacts LPS-induced ERK1/2 pathway activation via ABIN2 and TPL2 regulation. Notably, p38γ/δ knockout did not affect the instant activation of p38α and JNK1/2-induced by LPS(Risco, et al., 2012). Nonetheless, the exact mechanism underlying the p38γ/δ-regulated TPL2 and ABIN2 protein levels in macrophages are yet to be elucidated.

The simultaneous activities of p38γ and p38δ proteins at various levels jointly regulate the expression of inflammatory cytokines, and this process is implemented by regulating the expression of signaling pathway constituents required by cytokine production during the immune response or by directly regulating the cytokine transcription (Risco, et al., 2012). p38γ and p38δ are the therapeutic targets that might putatively eliminate the side effects of various p38α inhibitors as assessed in on-going sepsis and rheumatoid arthritis trials(Cohen, 2009; Genovese, 2009). Hitherto, TPL2 has become an attractive target for anti-inflammation therapy, and p38γ and p38δ also participate in the inflammatory response. Therefore, we could evaluate the feasibility of these druggable targets with respect to inflammatory diseases.

3.4. TPL2 regulates PI3K-Akt-mTOR-p70 S6k signaling pathway

A majority of the TLRs activate PI3K-Akt-mTOR-p70 S6k signaling pathway, which is a negative regulator for LPS-induced phosphorylation of p38a, JNK, and ERK1/2. Moreover, this pathway promotes IkBα expression and downregulates the phosphorylated forms of p38a, JNK, and ERK1/2 in TLR-activated macrophages by suppressing the MyD88-dependent activation pathway(Weichhart and Saemann, 2009; Guha and Mackman, 2002; Fukao and Koyasu, 2003). Furthermore, TPL2 increases the phosphorylation of Akt Ser473 residue and p70S6K Thr389 in LPS-stimulated macrophages and promotes IkBα expression while decreasing the NOS2 expression. This phenomenon is confirmed by dampened phosphorylation of Akt and p70S6K in TPL2-/- cells (Richardson, et al., 2015).

TPL2 regulates IFN-α/β and IFN-γ; however, it is required for inducing IFN-γ production. TPL2 acts as a positive regulator for IFN-γ production in plasmacytoid dendritic cells via activated ERK and PI3K/mTOR/Akt pathways. When dendritic cells are pre-treated with rapamycin (mTOR inhibitor), LY294002 (PI3K inhibitor), or U0126 (MEK inhibitor) prior to TLR stimulation, IFN-γ expression levels are lowered, equivalent to the counterpart detected in TPL2-/- cells, thereby confirming that ERK, PI3K, or mTOR signal transduction favors IFN-γ production in dendritic cells(Kuriakose, et al., 2015).

4. TPL2 regulates innate immune cells

4.1. TPL2 regulates the differentiation of CD4 + T cells

CD4 + T cells differentiate into different Th lineages as directed by different cytokines. Th1 cells express T-bet and produce IFN-γ to exert a protective effect against intracellular pathogens. Th2 cells express GATA3 and secrete IL-4, IL-5, and IL-13. Th17 cells express ROR-γt and produce IL-17 and IL-22 to eliminate the extracellular pathogens. T regulatory cells (Tregs) express FoxP3 and produce anti-inflammatory cytokines, including IL-10, IL-35, and TGF-β, to inhibit the pro-inflammatory immune response and maintain immune tolerance (Kanhere, et al., 2012; Zhu and Paul, 2008) (Fig. 4). TPL2 plays a major role in the above cell differentiation.

TPL2 is a serine/threonine kinase that regulates Th1 polarization and secretion of the inflammatory cytokine, IFN-γ, which plays a critical role in host resistance to intracellular pathogens. After infecting the bone marrow chimeras with *Citrobacter rodentium*, TPL2-/- T cells exhibited significantly low expression of IFN-γ than wild-type T cells

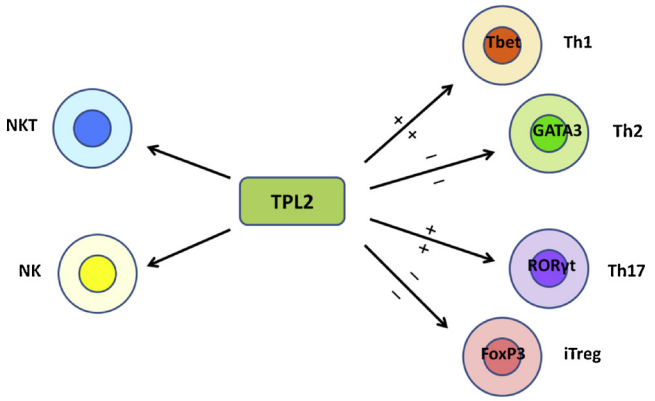

Fig. 4. TPL2 regulates innate immune cells. TPL2 regulates the differentiation of CD4 + T cells into different T helper (Th) lineages under the guidance of different cytokine signaling. TPL2 promotes differentiation of CD4 + T cells into T-bet-expressing Th1 cells and produces IFN-γ to provide protection against intracellular pathogens. TPL2 inhibits CD4 + T cell differentiation into GATA3-expressing Th2 cells and produces IL-4, IL-5 and IL-13, these are key molecules in humoral immunity. TPL2 promotes differentiation of CD4 + T cells into Th17 cells expressing ROR-γt and produces IL-17 and IL-22 to clear extracellular pathogen infections. TPL2 inhibits CD4 + T cell differentiation into regulatory T cells (Treg) expressing FoxP3 and produces anti-inflammatory cytokines IL-10, IL-35 and TGF-β, inhibiting pro-inflammatory immune responses and maintaining immune tolerance. TPL2 is still important participants in the differentiation of CD4 + T cells into NK and NKT cells.

from the same host (Acuff, et al., 2017). Moreover, during infection, lamina propria TPL2-/-/CD4 + T cells could not differentiate into IFN-γ-producing Th1 cells, indicating the crucial role of TPL2 in Th1 polarization. Conversely, a recent study demonstrated that genetic blocking of ERK pathway in TPL2-/- macrophages prompted Th1 polarization in antigen-specific CD4 + T cells infected with Mycobacterium tuberculosis, resulting in increased production of IFN-γ (Richardson, et al., 2015).

Th17 cells are CD4 + T cells producing IL-17A, IL-17 F, IL-21, and IL-22, which can recruit neutrophils for help in eliminating pathogens (Roussel, et al., 2010; Miyamoto, et al., 2003; Griffin, et al., 2012). Th17 effector cytokines are essential for eliminating the extracellular bacteria and fungi. Reportedly, TPL2 promoted Th1 polarization and IFN-γ production in vivo and in vitro (Watford, et al., 2008), as well as Th17 cell differentiation and IL-17A secretion in vitro. As a result, the IL-17A content in TPL2-/- T cells was significantly less than that in wild-type T cells from the same host (Acuff, et al., 2017), validating the auxiliary effect of TPL2 on Th17 differentiation and IL-17A expression. Furthermore, TPL2 inhibits FoxP3 expression by activating the MEK-ERK pathway (Acuff, et al., 2015). Th17 differentiation is negatively regulated by transcription factor FoxP3, and TGFβ-induced FoxP3 expression is increased in TPL2-/- Th17 cells, thereby inhibiting the expression of IL-17A.

Tregs ae a subset of T cells, expressing FoxP3 and presenting immune suppression, which in turn, maintains the peripheral tolerance via limiting the immune response to autoantigens(Li, et al., 2016). Owing to the pro-inflammatory effect, TPL2 is preliminarily postulated to antagonize the differentiation of immune suppressive Tregs (Bilate and Lafaille, 2012). Both classes of FoxP3+ Tregs exhibit immunoregulation, playing a vital role in preventing against autoimmune diseases. Tregs differentiation is the result of coordination between the intrinsic factors (such as TCR signal transduction pathway) and the extrinsic factors (such as co-stimulation or cytokine signals provided by helper cells) of T cells (Li, et al., 2016; Bilate and Lafaille, 2012; Belkaid and Oldenhove, 2008). TCR acts in synergy with the co-stimulation of molecules and cytokines (TGFβ and IL-2) that activate Foxp3 transcription. Thus, TCR signal combined with cytokine IL-2 and TGF activate the Foxp3 transcription in iTreg differentiation (Davidson, et al., 2007). TPL2 generally constrains the differentiation and proliferation of Tregs by the instability of Treg lineage via the MEK-ERK-suppressed binding activity of FoxP3 with target DNA. Thus, the activation of an AKT-mTOR-S6 pathway inhibits the FoxP3 expression and CTLA-4 induction (CTLA-4 is a co-suppressor highly expressed in FoxP3+ Tregs to maintain the immune suppression function) during Tregs conversion (Haxhinasto, et al., 2008). In addition, the AKT-mTOR-S6 pathway is also a TCR signal axis for the negative regulation of iTreg differentiation. As a result of TPL2 gene knockout, attenuated mTOR signal transduction favors iTreg differentiation.

4.2. TPL2 regulates NK cells

Natural killer T cells (NKT) constitute a subset of innate immune T lymphocytes. TPL2 coordinates the production of effector cytokines in NKT cells via ERK and Akt signal transduction (Vyrla, et al., 2016), which in turn, activates the NKT cells and produce excessive immunoregulatory molecules, including Th1 cytokine IFN-γ and Th2 cytokine IL-4, and both cytokines play a pivotal role in immunoregulation via liver cytotoxicity (Kaneko, et al., 2000) and neutrophil infiltration (Jaruga, et al., 2003). The application of TPL2 inhibitor to suppress MEK or PI3K could reduce the IL-4 secretion, and simultaneously inhibit the IFN-γ production. Previous studies delineated TPL2 kinase as a key signaling molecule as the primary mediator in iNKT cells and liver inflammation. In addition, while modulating the liver inflammation, it coordinates the production of effector cytokines in NKT cells via ERK and Akt signal transduction (Vyrla, et al., 2016). These findings have elucidated the mechanism underlying NKT cell activation.

The previous researches demonstrated IL-12-induced IFN-γ production in CD4 + T cells in an aTPL2-dependent manner (Watford, et al., 2008). Conversely, IFN-γ production in NK cells was independent of TPL2 activation. STAT4 is a transcription factor that is an essential factor for IL-12-induced IFN-γ production. Interestingly, the expression of STAT4 is low in T cells and dependent on the stimulation by TPL2-ERK pathway, whereas that in NK cells is high and independent of TPL2 under the naive state. Moreover, the high expression of STAT4 in NK cells is associated with their direct response to IL-12 stimulation, resulting in IFN-γ secretion (Fostel, et al., 2006). The above research results indicated that TPL2 is one of the critical factor in NK cell physiology and innate immunity.

5. Conclusion and prospects

The advanced studies have thoroughly elucidated the roles of TPL2 in innate immune, inflammation, tumor, and cancer. The future study direction is to identify how TPL2-induced cytokine production and the host immune response to pathogens. Several studies have proved that TPL2 signal transduction is specific to cell types and stimulation classes, and thus, it is a novel and promising target for inflammation and malignancy therapeutics. Hitherto, no TPL2 inhibitors have been developed and marketed successfully thereby necessitating further studies with respect to the safety and reliability towards TPL2. Finally, it can be predicted that TPL2-regulated innate immune response via the innate immune signaling pathway and innate immune cell differentiation would become a research hotspot.

Conflict interest

No conflict of interest exits in the submission of this manuscript, and manuscript is approved by all authors for publication.

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