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REVIEW

TTP-mediated regulation of mRNA stability in immune cells contributes to adaptive immunity, immune tolerance and clinical applications

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ABSTRACT

Dendritic cells (DCs) form a sentinel network to induce protective immunity against pathogens or self-tolerance. mRNA stability is an important part of the post-transcriptional regulation (PTR) that controls the maturation and function of DCs. In this review, we summarize the effects of TTP-mediated regulation of mRNA stability in DCs, focusing on DC maturation and antigen presentation, T cell activation and differentiation, immune tolerance and inflammation. We also discuss the potential DC-based immune treatment for HIV^+ patients through regulation of mRNA stability. This review proposes the regulation of mRNA stability as a novel immune therapy for various inflammatory diseases, such as arthritis and dermatitis.

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1. Introduction

After the capture of pathogens, immature dendritic cells (DCs) migrate to lymph nodes, where they become mature DCs and present antigens to T cells [1–3], which induce the differentiation of naïve T cells into effector T cells [4]. In addition, DCs play a major role in the maintenance of central tolerance and peripheral tolerance [5,6]. When thymocytes are presented with self-antigens, DCs induce negative selection, which leads to central tolerance [6]. The mechanism of peripheral tolerance established by DCs towards tissue-associated self-antigens involves the PD-L1 /PD1 interaction between DCs and T cells, resulting in the generation of antigen-specific peripheral iTregs [6].

Accumulating studies have indicated that the regulation of key gene expression, including transcriptional and post-transcriptional regulation (PTR), is crucial in the maturation and function of DCs [7,8]. The transcriptional control of DCs has been well studied [7]; however, the underlying mechanism of PTR is not fully understood. Over the past decade, researchers have focused on miRNA-mediated PTR in DCs [9]. However, except for the ARE-associated RNA binding protein (RBP) tristetraprolin (TTP), few studies focus on the PTR mediated by RBPs in DCs. TTP (also known as TIS11, Zfp36, and Nup475), encoded by the gene Zfp36, contains two zinc finger domains, a C-terminal domain and a N-terminal domain, which plays a vital role in the post-transcriptional regulation of inflammatory responses [10–12]. The two zinc finger domains within TTP recognize specific AREs, such as UUAUUUAUU, in the 3′-UTR of the target mRNA [13]. Studies demonstrated that TTP recruits the CCR4-NOT complex via its C-terminal domain to remove the poly(A) tail at the 3′ end [14] and recruits decapping factors, including Dcp2, Dcp1a, Edc3 and Hedls, via its N-terminal domain [12]. However, the order of recruitment of these proteins has not been determined. Interestingly, TTP also recognizes and binds to motifs with ARE-like sequences or even without AREs in DCs, but the mechanism requires further research [3]. In general, TTP dephosphorylation leads to stronger binding to the ARE and causes mRNA degradation [15]. However, the robust binding targets of TTP in macrophages and T cells, such as IL-1β, Sdc4, Ifng, and Cd69, showed little decrease at the level of mRNA stability, indicating that the binding of TTP is important but not sufficient for mRNA destabilization in macrophages and T cells [16,17]. In addition to regulating mRNA stability, translational inhibition is an important part of TTP-mediated PTR of gene expression [18–20].

Herein, we summarize and discuss the effects of TTP-mediated regulation of mRNA stability in DCs, focusing on DC maturation, antigen presentation, T cell activation and differentiation, and immune tolerance. We also discuss the target mRNAs of several potential RBPs, including HuR, Regnase-1 and Roquin (Fig. 1). In addition to TTP, the role

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of RBPs such as HuR, Regnase-1 and Roquin in T cells have been extensively discussed [21], so we discuss the effects of TTP-mediated regulation of mRNA stability on T cells.

These findings may help us to understand DC-mediated immune regulation in health and disease and provide potential therapeutic applications to treat various diseases, such as asthma [22] and psoriasis [23].

2. Effects of TTP on mRNA stability in DCs

2.1. TTP influences DC maturation by regulating mRNA stability in DCs

TNF-α induces the migration of immature DCs from peripheral sites into secondary lymphoid organs, where these cells become mature DCs that express high surface levels of MHC II and costimulatory molecules, enabling efficient T cell stimulation [24]. Silva-Cardoso et al. revealed that CXCL4-induced monocyte-derived DCs (moDCs) lacking TTP exhibit higher TNF mRNA stability than their wild-type (WT) counterparts, which indicates that TTP inhibits TNF production and prevents DC maturation by mediating TNF mRNA decay [25] (Fig. 1).

2.2. TTP influences antigen presentation of DCs by regulating mRNA stability in DCs

MHC I is formed by a heavy chain (α chain) that is encoded by an MHC I gene and a light chain (β 2 microglobulin) that

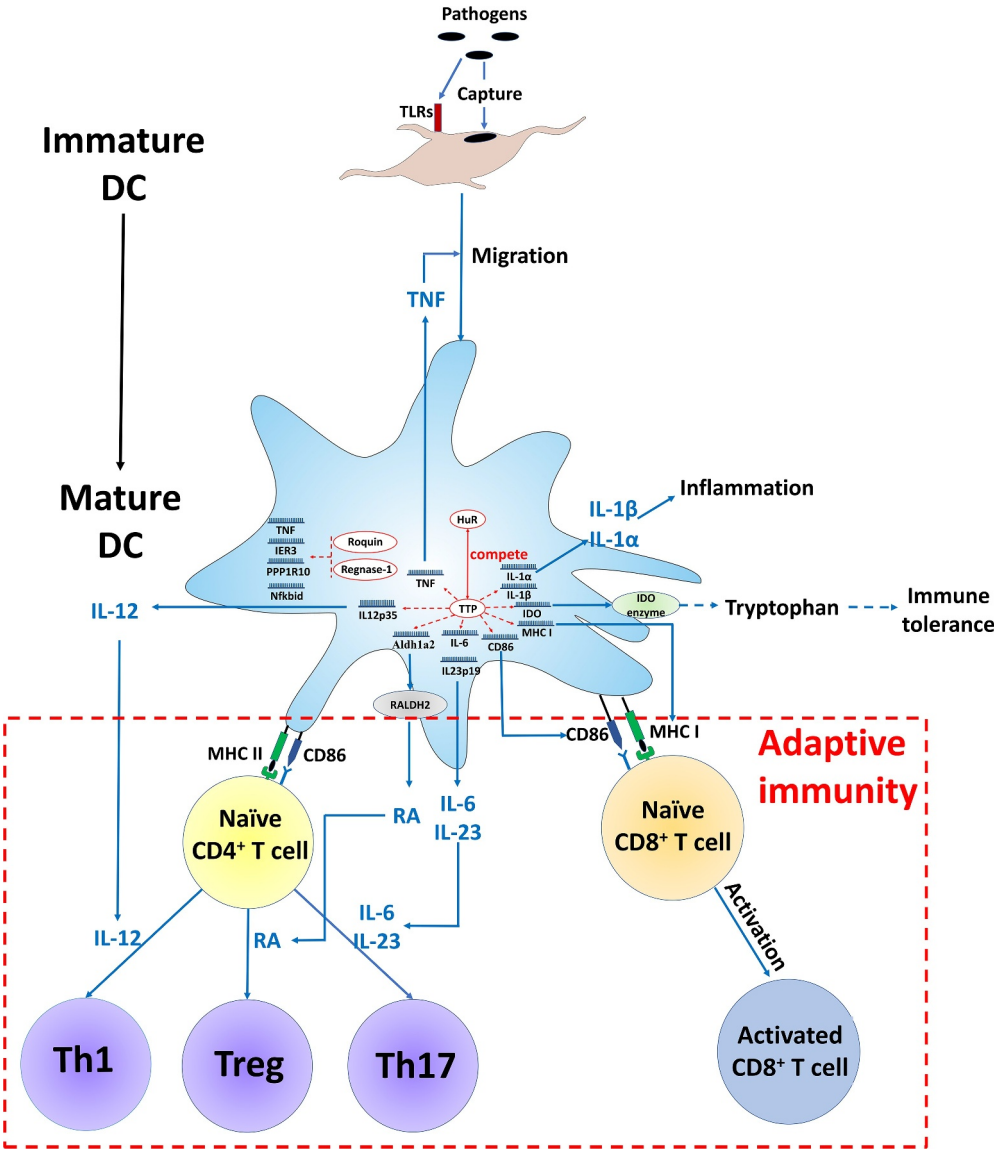

Figure 1. TTP-mediated regulation of mRNA stability in DCs. After the capture of pathogens, immature DCs migrate to secondary lymphoid organs and become mature DCs that express high levels of MHC I, MHC II and CD86. When antigenic peptides are presented to naïve $CD8^+$ T cells through MHC I, naïve $CD8^+$ T cells are activated and become activated $CD8^+$ T cells. when antigenic peptides are presented to naïve $CD4^+$ T cells through MHC II, naïve $CD4^+$ T cells are then activated and differentiate into Th1 cells, Tregs or Th17 cells in response to different cytokines. mature DCs secrete TNF to promote the migration of immature DCs, IL-6 and IL-23 to promote Th17 cell differentiation, IL-12 to promote Th1 cell differentiation, RA to promote Treg differentiation and IL-1β to promote inflammation. Aldh1a2 encodes the RA-producing protein RALDH2 and promotes the secretion of RA. the enzyme IDO decreases the concentration of tryptophan and causes immune tolerance. TTP destabilizes Aldh1a2, IL-6, IL-23, IL-12, TNF, IDO, MHC I, CD86 and IL-1β mRNA. Roquin and Reganse-1 potentially destabilize TNF, IER3, PPP1R10 and Nfkbid mRNA in DCs. Dashed arrows indicate the inhibitory effect on the target or the destabilizing effect on the target mRNA. solid arrows indicate the promotional effect on the target. solid double arrows indicate HuR and TTP potentially competing for binding site in DCs. molecular interactions are explained in the text.

is encoded by a non-MHC I gene [26]. DCs gather antigens and present them to $CD8^+$ T cells in the form of MHC I-bound peptides [27]. A cell that is infected with virus or expressing mutated genes will display antigenic peptides, which allows $CD8^+$ effector T cells to identify and eliminate these cells [27].

Emmons et al. showed that TTP specifically binds and destabilizes MHC I mRNA in DCs [3]. However, MHC I is not in the ARE database and does not contain 'ARE-like' sequences in the 3′-UTR [3] (Fig. 1). We suggest that TTP regulates MHC I expression via a non-ARE-dependent mechanism and inhibits antigen presentation by DCs, which requires further research.

2.3. TTP influences DC-mediated T cell activation by regulating mRNA stability in DCs

There are two signals required for T cell activation: recognition of peptide antigens presented by MHCs (signal 1) and costimulation through CD28 binding to CD80 or CD86 expressed by antigen-presenting cells (APCs) (signal 2) [28]. Studies have shown that CD86 is upregulated upon DC maturation and plays a critical role in the amplification of T cell responses [3,29–32].

Although CD86 is not in the ARE database, it contains two ARE-like sequences: (nucleotides 1583–1589) UAUUUAU and (nucleotides 2552–2560) UUAUUUUAU [3]. Emmons et al. showed that TTP transfection reduced luciferase expression of the CD86 3′-UTR that contained ARE-like sequences [3], which could inhibit T cell activation (Fig. 1).

2.4. TTP likely influences DC-mediated T cell differentiation by regulating mRNA stability in DCs

The differentiation of naïve $CD4^+$ T cells into T helper (Th)17 or Th1 cells is controlled by interactions with DCs and mediated by cytokines produced by DCs [33]. Previous studies have shown that DCs produce IFN-γ and IL-12 to promote Th1 cell differentiation and TGF-β, IL-1, IL-6 and IL-23 to promote Th17 cell differentiation [33–38]. In addition to cytokines, retinoic acid (RA) secreted by DCs promotes the differentiation of regulatory T cells (Tregs). These processes are posttranscriptionally regulated by TTP through mRNA decay. Herein, we summarize the modulatory effects of TTP on DC-induced T cell differentiation and the impact on the adaptive immune response (Fig. 1).

2.4.1 Th17 cells

IL-23 and IL-6 promote the differentiation of Th17 cells, which plays a crucial role in the development of immune diseases, such as atopic dermatitis and arthritis [39–42].

IL-23 is composed of an IL23p40 subunit and an IL23p19 subunit and can be secreted by DCs [43]. Qian et al. revealed that TTP knockout (KO) mice exhibit increased IL23p19 mRNA stability in bone marrow-derived DCs (BMDCs) and exacerbated dermatitis [44]. To further examine the mechanism, Molle and colleagues depleted CAF1, a poly(A) nuclease complex required for TTP-mediated mRNA decay [45], by knocking down the CNOT7 gene and observed increased mRNA levels of IL23p19, indicating that TTP may mediate IL23p19 mRNA decay through CAF1-dependent deadenylation in BMDCs [42] (Fig. 1). To assess the binding site of TTP that controls IL23p19 mRNA, Molle et al. showed that IL23p19 mRNA contained five AREs within its 3′-UTR, four of which were conserved [42]. Site-directed mutagenesis revealed that all five AREs had to be mutated to completely abrogate the destabilizing effect of TTP, suggesting that all of them were involved in TTP-mediated regulation in DCs [42]. The binding of TTP to IL23p19 mRNA is regulated by IFN-γ and p38 MAPK signalling pathway activation. Upon inflammatory stimulation, the p38 MAPK signalling pathway is activated, which leads to the phosphorylation and inactivation of TTP, which inhibits the binding of TTP to IL23p19 mRNA in DCs [44,46–48]. IFN-γ inhibits p38 phosphorylation and causes TTP protein dephosphorylation, which could result in stronger binding of TTP to IL23p19 mRNA in DCs [44].

IL-6 produced by DCs promotes the differentiation of Th17 cells [41]. Silva-Cardoso et al. revealed that CXCL4-induced moDCs lacking TTP exhibited higher IL-6 mRNA stability than their WT counterparts [25]. We speculate that TTP inhibits Th17 cell differentiation by mediating IL-6 mRNA decay in CXCL4-induced moDCs.

2.4.2 Th1 cells

IL-12 is composed of an IL12p40 subunit and an IL12p35 subunit, can be secreted by DCs, is required for the development of innate and adaptive responses to intracellular pathogens by promoting naïve $CD4^+$ T cell differentiation into Th1 cells [49]. Molle et al. observed higher IL12p35 mRNA levels in TTP-KO BMDCs than in WT BMDCs [42]. We speculate that TTP inhibits Th1 cell differentiation by mediating IL-12 mRNA decay in BMDCs (Fig. 1). In addition, a p38 MAPK inhibitor accelerated IL12p35 mRNA decay in a TTP-dependent manner, suggesting that p38-MAPK-mediated inhibition of TTP modulated IL12p35 mRNA decay in BMDCs [42].

2.4.3 Tregs

TTP-KO mice exhibited increased inflammatory markers and developed 'TTP deficiency syndrome', including arthritis, dermatitis and conjunctivitis [50–52]. However, researchers found that DC-specific TTP KO did not cause a spontaneous phenotype in mice, such as local and systemic inflammation [53]. La et al. further found that DC-specific TTP KO mice exhibited expansion of Tregs, which led to the suppression of inflammation [52]. A previous study showed that DCs promoted the transformation of primitive $CD4^+$ T cells to Tregs in the gut by producing RA [54]. The researchers further found that TTP mediated Aldh1a2 [which encodes RA-producing protein retinaldehyde dehydrogenase 2 (RALDH2)] mRNA decay in DCs by binding to the ARE, which inhibited primitive $CD4^+$ T cell differentiation into Tregs [52] (Fig. 1).

2.5. TTP influences IL-1β mediated inflammation by regulating mRNA stability in DCs

IL-1β is mainly secreted by immune cells types, such as macrophages and DCs, and is associated with autoimmune diseases, nonresolving inflammation and cancer [51,55–57]. Sneezum et al. found that TTP bound to IL-1β mRNA but was unable to destabilize it in macrophages [51]. However, increased IL-1β mRNA levels and enhanced production of IL-1β cytokines was found in TTP KO BMDCs compared to WT cells, indicating that TTP bound to and destabilized IL-1β mRNA [51] (Fig. 1).

IL-1 type-1 receptor (IL-1R1) is the main receptor for IL-1β and is expressed by various cell types, including innate and adaptive immune cell types [58]. The researchers then deleted IL-1R1 in TTP KO mice and found delayed onset and reduced severity of 'TTP deficiency syndrome', indicating the importance of TTP-mediated regulation of IL-1β mRNA stability in immune homoeostasis [51].

2.6. TTP influences immune tolerance by regulating mRNA stability in DCs

The enzyme IDO is a potent suppressor of T cell responses and promotes tolerance by decreasing the local concentration of tryptophan, an amino acid that is crucial for the proliferation and differentiation of T cells [59]. RNA immunoprecipitation and microarray analysis (RIP-Chip) results demonstrated that IDO was the target of TTP in DCs [3]. Moreover, BMDCs from TTP KO mice exhibited higher IDO mRNA expression than their WT counterparts in published RNA-seq results [51]. Thus, we speculate that TTP mediates IDO mRNA decay in DCs to inhibit immune tolerance (Fig. 1).

2.7. Clinical applications of TTP-mediated regulation of mRNA stability in DCs

There are two theories on the role of DCs in HIV infection. The first theory is that DC subsets need to become infected with HIV to mediate viral spread. The second theory indicates that DC subsets simply carry HIV to enable safe passage and transfer of the virus to a secondary lymph node to infect $CD4^+$ T cells [60].

TTP can inhibit HIV-1 replication by binding to the AU-rich sequence of HIV-1 RNAs [61]. TTP may inhibit HIV-1 replication by mediating HIV-1 mRNA decay, since CCR4-NOT complex 1 (CNOT1), a deadenylation complex that binds to the C-terminus of TTP and induces mRNA decay, is associated with the response to DC-based immune treatment in HIV^+ patients [14,62,63].

2.8. Negative feedback loop of TTP in DCs

The expression of TTP is affected by negative feedback mechanisms [64–66]. In moDCs exposed to CXCL4, Silva-Cardoso et al. found increased TTP mRNA stability caused by the phosphorylation of TTP, indicating that TTP was able to destabilize its own mRNA [25] (Fig. 1).

3. Potential effects of HuR on mRNA stability in DCs

HuR is a member of the Elav/Hu family and contains three RNA-recognition motifs (RRM) [67], which can selectively bind to the ARE [68–70]. The third domain (RRM3) simultaneously binds to the poly(A) tail, which protects the poly(A) tail from poly(A) exonuclease [69,71]. Interestingly, studies showed that HuR and TTP compete for the same AU-rich sequence but have opposing effects on mRNA stability [72,73] (Fig. 1). Further study is required to validate the targets of HuR in mRNA stability in DCs.

4. Potential targets of Regnase-1 and Roquin in mRNA stability in DCs

Regnase-1, also known as Zc3h12a or MCPIP1, specifically recognizes the stem-loop structure and is responsible for mRNA decay by inducing endonucleolytic cleavage [74] . The E3 ubiquitin ligase Roquin, encoded by the Rc3h1 gene, specifically recognizes the stem-loop structure and mediates the degradation of mRNA transcripts through the recruitment of the CCR4-NOT deadenylase complex [75,76].

De novo prediction of secondary structure motifs in 3′ UTRs in DCs performed by Kumagai and colleagues showed that TNF, IER3, PPP1R10 and Nfkbid contained stem-loop structures almost identical to that of Regnase-1 targets and Roquin targets, suggesting a potential role of Regnase-1 and Roquin in regulating mRNA stability in DCs [77,78] (Fig. 1). Further in vivo study is required to clarify the effects of Reganse-1-mediated mRNA decay and Roquin-mediated mRNA decay in DCs.

5. Effects of TTP on mRNA stability in T cells

5.1. Primary T cells

IL-22, a member of the IL-10 cytokine family, is produced by lymphoid cells such as $CD4^+$ or $CD8^+$ T cells and protects tissues in infection- and injury-driven diseases at biological barriers including the intestine, lung and liver [79,80]. Increased IL-22 production was found in TTP KO mice due to increased IL-22 mRNA stability in primary T cells [79].

5.2. Activated T cells

Interferon-γ (IFN-γ) and IL-2 are critical T cell-derived cytokines that play key roles in immune responses by inducing activation, proliferation and differentiation of T cells [81–83]. In activated T cells from TTP KO mice, Ogilvie et al. found increased IFN-γ and IL-2 production due to the stabilization of mRNA [84,85].

5.3. Th17 cells

IL-17 is a regulatory cytokine secreted by immune cells, such as Th17 cells and plays a central role in the development of autoimmune diseases, such as multiple sclerosis and rheumatoid arthritis [86]. A previous study showed that TTP controls the function of Th17 cells by promoting IL-17 mRNA decay [87]. Peng's group further found that T cell-specific TTP-KO

mice suffered more severe DSS-induced intestinal inflammation and colitis than WT mice [88].

6. Conclusion and perspective

We summarize the effects of TTP-mediated regulation of mRNA stability in DCs, focusing on DC maturation, antigen presentation, T cell activation and differentiation, and immune tolerance. We also discuss the target mRNAs of several potential RBPs in DCs, such as HuR, Regnase-1 and Roquin (Fig. 1). Moreover, we summarize the effects of TTP on mRNA stability in T cells.

Other potential targets of TTP require further research. In addition to the regulatory role of TTP in the adaptive immune response, further studies are required to identify its role in the innate immune response, such as in the capture of pathogens. Interestingly, real-time PCR performed by Jillian Emmons and colleagues showed that TTP specifically bound to the mRNA of CCL-13, CSTA, PSPA, REA, RHO, S100A6, snRPD, SOD2, and ZN2216 in DCs [3]. However, the roles of these mRNAs in the DC-mediated immune response requires further research.

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Disclosure statement

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