Regulated changes in mRNA stability are critical drivers of gene expression adaptations to immunological cues. mRNA stability is controlled mainly by RNA-binding proteins (RBPs) which can directly cleave mRNA but more often act as adaptors for the recruitment of the RNA-degradation machinery. One of the most prominent RBPs with regulatory roles in the immune system is tristetraprolin (TTP). TTP targets mainly inflammation-associated mRNAs for degradation and is indispensable for the resolution of inflammation as well as the maintenance of immune homeostasis. Recent advances in the transcriptome-wide knowledge of mRNA expression and decay rates together with TTP binding sites in the target mRNAs revealed important limitations in our understanding of molecular mechanisms of TTP action. Such orthogonal analyses lead to the discovery that TTP binding destabilizes some bound mRNAs but not others in the same cell. Moreover, comparisons of various immune cells indicated that an mRNA can be destabilized by TTP in one cell type while it remains stable in a different cell lineage despite the presence of TTP. The action of TTP extends from mRNA destabilization to inhibition of translation in a subset of targets. This article will discuss these unexpected context-dependent functions and their implications for the regulation of immune responses. Attention will be also payed to new insights into the role of TTP in physiology and tissue homeostasis.

Keywords: tristetraprolin (TTP), zinc finger protein 36 (Zfp36), RNA binding protein, mRNA stability/decay, inflammation, immune system, immune homeostasis

INTRODUCTION

It is now well accepted that regulation of mRNA stability by RNA-binding proteins (RBPs) is indispensable for healthy immune responses. RBPs orchestrate the immune system by modulating gene expression through mRNA destabilization or stabilization, or by controlling translation (1–3). Although this basic knowledge is established, many important questions remain unresolved.
These include mechanistic explanations of the phenotype caused by an RBP deletion in mice and the selective functions of RBPs in specific cell types despite ubiquitous expression. Improved models of the molecular mechanisms of RBP action are needed to answer the open questions. These models will likely abandon the linear schemes in which RBP binding to a target mRNA inevitably results in a canonical consequence, e.g. mRNA decay. The aim of this review is to provide a framework for updated models of RBP action in immune responses.

The history of mRNA decay research, both at the level of mechanisms and functions, is tightly connected to the immune system. The first evidence that selective mRNA degradation is driven by a cis-acting element was reported for the mRNA encoding the granulocyte/monocyte growth factor GM-CSF (4). This study established that an adenylate-uridylate-rich element (AU-rich element; ARE) in the 3’ untranslated region (3’ UTR) of the GM-CSF mRNA (encoded by the CSF2 gene) confers mRNA instability if introduced into the 3’ UTR of a stable mRNA. The autonomous effect of AREs on mRNA stability has been subsequently documented for many other mRNAs. The key role of ARE-dependent mRNA decay in vivo was revealed by the deletion of the ARE in the mouse TNF gene which resulted in a spontaneous development of gut and joint inflammation (5). However, genome sequencing and transcriptome-wide mRNA stability assays indicated that the initial model of an autonomous function of 3’ UTR-located AREs in mRNA destabilization was too simple. Approximately 20% of human genes contain AREs in their 3’ UTRs, yet most of the corresponding mRNAs are stable (6, 7). The medium half-life of mRNA in human HepG3 cells is approximately 10 h with mRNAs of metabolic genes having on average the highest half-lives (6). In comparison, inflammation-associated mRNAs belong to those with the shortest average half-lives. For illustration, the decay rate of TNF mRNA is in the range of 20 – 40 min, depending on the cell type and stimulus (8, 9). Although inflammation-induced mRNAs are enriched in AREs, it is now accepted that the presence of an ARE is not sufficient to destabilize the mRNA. Hence, new and more comprehensive models of regulation of mRNA decay by cis-acting elements are needed.

MECHANISMS OF RBP-DRIVEN CHANGES IN mRNA STABILITY

mRNA destabilizing RBPs bind and facilitate the target mRNA degradation in two ways, depending on the properties of the particular RBP (1, 2, 10, 11). One class of RBPs possesses an endonuclease activity which allows the RBP to cleave the target mRNA and generate ends devoid of the 5’ m7G cap and the 3’ poly(A) tail. These unprotected ends serve as substrates for exonucleases which process the mRNA in 3’ – 5’ direction via the exosome and 5’– 3’ direction via XRN1 (12, 13). The best characterized endonucleolytic RBP relevant for the immune system is Regnase-1 (gene name Zc3h12a) which destabilizes mRNAs of transcription factors and cytokines such as Icos, Ox40, c-Rel, IL-2 and IL-6 (14). Regnase-1-deficient mice show severe systemic inflammation associated with T and B cell activation. The phenotype is largely recapitulated by a T cell-specific deletion (14). The second class of RBPs destabilize the target mRNA by promoting the recruitment of the CCR4-NOT deadenylase and the DCP1/DCP2-containing decapping complexes (15, 16). A number of RBPs in this class are known to regulate the immune system. Tristetraprolin (TTP), as one of the most prominent members, will be described in detail below. Other well characterized members are Roquin-1 (gene name Rc3h1), Roquin-2 (Rc3h2), Zfp36l1, Zfp36l2 and Aup1. The Roquin proteins redundantly target the mRNAs of Icos and Ox40 to control T cell activation. Deletion of both Roquin-1 and Roquin-2 genes specifically in CD4 T cells results in an autoimmune phenotype resembling systemic lupus erythematosus while deletion of the single genes remains without severe consequences (17). The proteins Zfp36l1 and Zfp36l2 are members of the TTP family but, in contrast to TTP, have more pleotropic functions as demonstrated by embryonic or postnatal lethality of the respective knockouts in mice (18, 19). Zfp36l1 and Zfp36l2 are involved in the regulation of immune system in multiple ways. They control the expression of proliferative cell cycle regulators during B and T cell development: double deletion of Zfp36l1 and Zfp36l2 in T cells results in lymphopenia and malignant transformation of immature CD8 T cells while similar deletion in pro-B cells causes a block in B cell development owing to a failure in entering quiescence hence genome safeguarding prior to VDJ recombination (20, 21). The protein Aup1 exhibits anti-inflammatory functions by promoting the degradation of cytokine mRNAs as revealed by the hypersensitivity of Aup1-deficient mice to endotoxic shock (22). Aup1 has been subsequently found to regulate many other processes in addition to immune responses including telomere maintenance and muscle regeneration (23, 24).

mRNA-stabilizing RBPs are less well understood and their functions are more pleiotropic as compared to the destabilizing RBPs such as TTP. The general opinion is that mRNA-stabilizing RBPs act by preventing the destabilizing proteins from binding to the target. As a consequence, the target mRNAs are more stable and/or more efficiently translated. mRNA-stabilizing RBPs regulating immune responses include HuR (gene name Elavl1) and Arid5a. Deletion of HuR or Arid5a in mice resulted in increased resistance to experimental autoimmune encephalomyelitis (25, 26). Furthermore, HuR is required for antibody production by B cells (27). HuR is involved in regulation of other processes including liver metabolism, cell proliferation and cancer (28–30).

RNA BINDING OF RBPs CONTROLLING mRNA STABILITY

RBPs bind to RNA through interactions of their RNA-binding domains with specific sequences or defined structural elements in the target mRNA. The most frequent RNA-binding domain in the
immunoregulatory RBPs is the C3H1 (Cys-Cys-Cys-His) zinc finger domain present for example in TTP, Zfp36l1 and Zfp36l2 (2, 31). Regnase and Roquin contain a C3H1 zinc finger and an additional RNA-binding domain: a PIN domain and a ROQ domain, respectively (32, 33). Auf1 and HuR bind to RNA through the RNA recognition motif (RRM) domains which occur in 2 or 3 repeats in these proteins (34, 35). Arid5a interacts with RNA via an ARID domain which is known to recognize DNA in other ARID domain-containing proteins (26, 36).

The target site in the RNA is defined by the RNA-binding domain. The C3H1 zinc finger present in TTP, Zfp36l1 and Zfp36l2 binds preferentially to AREs with the core sequence UAAAUAU although divergent target sites have been identified as well (9, 21, 37). A preference for AU-rich sequences shows also the ARID domain of Arid5a (26). The RRM domain of Auf1 recognizes U- and GU-rich stretches and, albeit less frequently, AREs (38). The RRM motif of HuR prefers U-rich sequences (9, 39, 40). The preference of these binding domains for AREs or U-rich sequences reflects the unstructured nature of such sequences: AREs and U-rich sequences in general do not adopt a secondary structure. In contrast, Regnase and Roquin bind to RNAs exhibiting stem-loop folds with the loop part formed by three bases with a pyrimidine–purine–pyrimidine sequence while the stem is more variable both in length (5–8 bases in each half of the stem) and sequence (41, 42).

Transcriptome-wide binding assays revealed that most of these RBPs bind frequently to 3′ UTR and, unexpectedly, introns (9, 21, 38–40). Binding to introns regulates splicing in case of HuR (40, 43). However, it appears that functional interactions are largely confined to elements located in the 3′ UTRs as intronic binding in general does not result in changes in stability or splicing of the transcript.

THE TTP PROTEIN FAMILY: EVOLUTI0NARY CONSERVED RBPs WITH DIVERSE FUNCTIONS FROM YEAST TO MAMMALS

TTP contains an RNA-binding domain formed by a characteristic tandem C3H1 zinc finger in the middle part and protein-protein interaction domains at the N- and C-termini (31). The tandem zinc finger and the overall domain structure are conserved in similar RBPs from yeast to plants and mammals hence these RBPs constitute the TTP protein family (44). Interestingly, no TTP protein members are found in birds despite their presence in reptiles (44). Although all these proteins facilitate mRNA degradation their functions in cells and/or organisms are diverse. For example, the yeast TTP family member Cth2 regulates mRNA stability upon iron deficiency while the Xenopus TTP proteins act during embryonic development and the C. elegans homologues are required for meiosis and oocyte production (45–47). Humans contain three TTP family members (Ztp36, Zfp36l1 and Zfp36l2) and mice express the Zfp36l3 member in addition. Much of what we now know about the functions of the TTP protein family has been learned from knockouts in mice carried out by the Blackshear laboratory. Deletion of Zfp36l1 (also known as BRF1 and TIS11b) is embryonic lethal because of failure in umbilical circulation resulting from absent fusion of the allantois with the chorion (18). Mice lacking Zfp36l2 (also known as BRF2 and TIS11D) die within a few weeks after birth due to a marked deficiency in hematopoiesis (19). Zfp36l3 is a paternally imprinted X chromosome gene which is likely involved in regulation of iron metabolism in the placenta; Zfp36l3 deletion results in decreased neonatal survival rates without obvious morphological aberrances in surviving offspring (48).

TTP: A TTP FAMILY MEMBER WITH UNIQUE SELECTIVITY FOR THE REGULATION OF IMMUNE RESPONSES

TTP (Zfp36) is an outstanding member of the TTP family as its function is remarkably specific and related to the regulation of immune responses. TTP knockout in mice results in systemic inflammation characterized by arthritis, dermatitis, conjunctivitis and cachexia (49). This so called TTP deficiency syndrome develops within approximately 8 weeks of birth and progressively worsens leading to death of most animals at around 6–8 months of age. TTP-deficient mice do not show any developmental abnormalities or health defects at birth; the mice are not fertile presumably owing to their poor health (49). The TTP deficiency syndrome was shown to be dependent on TNF signaling and mechanistically explained by increased stability of Tnf mRNA (49, 50). Subsequent studies established that the inflammatory disease of TTP-deficient mice is caused, albeit to variable extent, by increased stability of other cytokine and chemokine mRNAs as well, notably Il23, Ccl3, Il1a and Il1b mRNAs (51–53).

Given this multiple evidence for its indispensable role in the immune system, it comes with no surprise that TTP has become one of the best studied RBPs. However, many important questions remain open. For example, it is not well understood which cell types drive the inflammatory disease in TTP-deficient mice. Mice bearing LysM-Cre-driven deletion of TTP in dendritic cells remain with CD11c-Cre-driven deletion of TTP in myeloid cells are cells with arguably the highest TTP expression (54, 55). Although these mice exhibit lethal hypersensitivity to endotoxemic shock, the absence of a spontaneous inflammatory disease in these mice develops from psoriasis-like focal skin lesions containing neutrophilic infiltrates, indicating that persistent local inflammation can become systemic with time. The model of keratinocyte-specific TTP deletion suggests that TTP expression is particularly critical in barrier tissues, i.e. tissues constantly exposed to environmental cues. However, it is remarkable that the full-body TTP knockout mice remain without pathology in the intestinal or lung epithelium, i.e. the most prominent mucosal barriers. The absence of mucosal
inflammation in TTP-deficient mice suggests that TTP has more complex roles in these tissues. Such functional complexity is supported by findings showing that the lack of intestinal pathology in TTP knockout mice is associated with a local expansion of regulatory T cells (57). Moreover, Villin-Cre-driven TTP deletion in intestinal epithelial cells increases the resistance against dextran sulfate-induced colitis suggesting, that the lack of TTP might enhance the robustness of the intestinal barrier (58). Although the mechanism is yet to be determined, the improved mucosal barrier might be caused by accelerated tissue regeneration since these mice exhibit higher numbers of Goblet cells. These findings suggest that the absence of TTP augments proliferation signals that are commonly associated with inflammatory conditions. In agreement, skin inflammation caused by TTP deficiency in keratinocytes promotes tumorigenesis that appears to be causally associated with overproduction of the growth factor amphiregulin (59). Consistently, amphiregulin mRNA is a TTP target. However, TTP deficiency can cause increased cell numbers also by means of decreased apoptosis as shown for TTP-deficient neutrophils: neutrophils devoid of TTP express higher levels of the TTP target Mcl1 mRNA which codes for an anti-apoptotic factor particularly relevant for neutrophils (60). Interestingly, this effect pertains only to immunostimulated (e.g. pathogen-engaged) neutrophils, not to the circulating dormant neutrophil pool.

Cumulatively, the available animal models of TTP deficiency clearly indicate that the major function of TTP is to control the immune response. Although TTP restricts cell numbers in some cases, this function is also largely related to control of inflammation: (i) by ameliorating inflammation TTP prevents the expression of inflammation-associated growth factors or anti-apoptotic proteins, (ii) TTP directly targets the mRNAs of several inflammation-associated growth or anti-apoptotic factors. More studies directly investigating cells from tissues are needed to complete our understanding of TTP effects in vivo.

**mRNA DESTABILIZATION BY TTP**

TTP promotes mRNA decay through the recruitment of the CCR4-NOT deadenylase and the DCP1/DCP2 decapping complexes to the bound target. The N- and C-termini of TTP represent the protein-protein interaction domains in this process. The CCR4-NOT deadenylase complex interacts with the N- and C-terminal domains with the CNOT1 subunit being directly involved in binding to TTP (61–64). The DCP1 and DCP2 decapping protein complexes interact with the N-terminal TTP domain (62). Following decapping and deadenylation, the target mRNA is degraded through the 5′-3′ exonuclease Xrn1 and the 3′-5′ exonuclease of the exosome, respectively. The identification of these interactions suggested that TTP-mediated mRNA degradation is governed by a protein recruitment cascade. However, this model does not explain why many TTP-bound RNAs (including mRNAs and introns) are stable as shown by more recent studies (9, 65–67). The surprising findings of these studies delineate that the process of mRNA destabilization by TTP is more complex and dependent on yet unidentified regulatory mechanisms.

**TTP BINDING TO RNA**

Both zinc finger domains are required for interaction of TTP with RNA as mutation of either of them abrogates RNA binding (68). Moreover, mutation of the first zinc finger in the TTP locus in mice phenocopied the complete TTP deletion (69). This was a significant finding as it definitively proved that the function of TTP is entirely dependent on its RNA binding activity. Initial characterization of the motif recognized by TTP focused on the TNF mRNA, the first known TTP target: the motif is a 9-mer with the sequence UUAUUUAUU which is repeated several times in the TNF 3′ UTR (37, 70). Subsequent analysis of RNAs enriched in RNA immunoprecipitation assays suggested that TTP binds to AREs also in other target mRNAs (71). A precise genome-wide mapping of target sequences was generated by several CLIP-Seq (cross-linking immunoprecipitation-high-throughput sequencing) studies employing immune cells. Although these nucleotide resolution analyses confirmed the preference of TTP for the UUAUUUAUU sequence, they also provided several unexpected findings (9, 65–67). The studies showed that TTP binds also to sites that were divergent from the canonical TTP binding sequence as visualized in the searchable TTP Atlas (https://ttp-atlas.univie.ac.at) (9). Moreover, TTP binding was not limited to 3′ UTRs but was detected at sites located in 5′ UTRs, coding sequences and introns as well (Figure 1). Particularly striking was the high incidence of TTP binding to introns. Although the number of identified intronic binding sites was dependent on the CLIP-Seq method, the peak finding algorithm and experimental cell system, the studies convincingly established that TTP interacts with pre-mRNA in addition to mRNA. This finding implies that TTP can engage RNA interactions in the nucleus. The biological significance of the intronic binding remains to be determined as no effects on splicing or stability of the intron-bound RNA has so far been observed (9). Given the high frequency of TTP binding to introns it is possible that introns act as sponge to titrate away TTP molecules. This mechanism was reported for circular RNAs that function as sponge molecules for micro RNAs (72, 73). Similar to intronic binding, it is currently unclear whether interactions of TTP with 5′ UTRs or coding sequences entail changes in RNA processing.

The CLIP-Seq data show that functional TTP bindings sites are located in 3′ UTR. Remarkably, binding of TTP to 3′ UTR does not always cause destabilization of the target mRNA, as revealed in recent studies. This enigmatic and probably significant property of TTP is discussed further below.

**REGULATION OF TTP**

TTP function is regulated in multiple ways with many of them remaining poorly understood. Moreover, it is likely that some key
regulatory events are still not known. Comprehensive knowledge about the regulation of TTP is critical for our understanding of the remarkably selective function of TTP in the immune system and for the control of inflammation in general. TTP is regulated at the level of transcription, mRNA stability, protein stability and by posttranslational modifications (31, 74–76). As far as we can say, all these mechanisms are critical for the appropriate extent, timing and selectivity of TTP-driven mRNA degradation. They act in concert to allow the immune system launching an efficient but not exaggerated inflammatory response.

TTP mRNA levels are low under steady state conditions but dramatically induced in response to inflammatory stimuli which are mostly associated with stress signaling. The increase in TTP mRNA levels is achieved mostly by transcriptional induction and...
to some extent also through mRNA stabilization. As an immediate early gene, TTP is transcriptionally activated rapidly after stimulation. The activation signals include growth factors, cytokines such as TNF, IL-4, IL-10, or IFN-γ, and bacterial products e.g. LPS (50, 78–80). The transcription factors involved in the transcriptional upregulation were characterized in few instances: IFNs, IL-10 and IL-4 drive TTP expression through STAT1, STAT3 and STAT6, respectively (78–80). STAT1 employs a GAS (Gamma interferon activation site) element which is conserved in the TTP promoter in mice and humans (78). This GAS element is likely involved also in response to IL-4 and IL-10. The activating signals often synergize to achieve maximal induction of TTP (78, 79).

Stabilization of TTP mRNA by p38 MAPK signaling contributes to induction of TTP expression (81). TTP mRNA contains AREs which interact with TTP protein suggesting that autoregulation is the mechanism underlying the low TTP mRNA stability. TTP mRNA is indeed moderately more stable in TTP knock-in mice expressing the zinc finger-inactivated mutant (69).

A central aspect of the regulation of TTP levels in cells is the control of TTP protein stability. TTP is continuously degraded in a proteasome-dependent way which appears to proceed without ubiquitination and is likely to involve the intrinsically unfolded N- and/or C-terminal domains (82, 83). The mechanism of this important process is not resolved and its elucidation would significantly advance our understanding of protein degradation in general. TTP protein stability increases by orders of magnitude upon phosphorylation of S52 and S178 (in mouse coordinates) (82, 84). Phosphorylation of these two residues is brought about by MK2, a kinase that is activated by p38 MAPK. Although the p38 MAPK/MK2-driven phosphorylation of S52 and S178 increases TTP protein stability and thereby positively regulates TTP levels, it inhibits the mRNA-destabilization activity of TTP. This phosphorylation-dependent TTP inhibition probably results from a combination of several processes: (i) S52 and S178 phosphorylation causes association of TTP with 14-3-3 proteins thereby preventing relocation of TTP to stress granules and processing bodies, (ii) 14-3-3 protein binding promotes export of TTP from the nucleus, (iii) S52 and S178 phosphorylation decreases association of TTP with the CCR4-NOT deadenylase, and (iv) MK2-dependent TTP phosphorylation diminishes TTP binding to RNA (85–88).

Although the mechanistic details of the function of S52 and S178 phosphorylation are not fully understood, the biological consequences have been convincingly revealed by generation of double knock-in mice bearing S52A and S178A mutations in the TTP locus (89). These mice are unable to express high TTP protein levels, consistent with a rapid TTP protein degradation. Nevertheless, the mice are protected against LPS-induced systemic inflammation indicating that the S52A/S178A mutant acts as hyperactive TTP in vivo. The double knock-in mouse confirmed the previously proposed model of TTP function according to which p38 MAPK leads to accumulation of inactive (i.e. phosphorylated) TTP in the initial phase of inflammation. Later, i.e. in the resolution phase of inflammation, the gradual decrease of p38 MAPK activity releases TTP from its inhibited state thereby facilitating degradation of TTP target mRNAs (9, 55). In parallel, the diminishing phosphorylation accelerates proteasomal degradation of TTP rendering the cells responsive to a new inflammatory stimulus.

TTP contains more than 30 phosphorylation sites out of which only S52 and S178 have been functionally annotated in cells and animals (90). A recent quest for a better understanding of TTP phosphorylation has revealed MK2-dependent phosphorylation of T84, S85, T250, and S316 out of which the phosphorylation of S316 is the most robust one (91). Notably, S316 phosphorylation in not involved in regulation of TTP protein stability; instead, it appears to regulate interactions of TTP with the translation inhibition proteins (91). It will be exciting to see the progress in functional characterization of other phosphorylation sites as they likely impinge on TTP in unexpected ways.

### TO DEGRADE OR NOT TO DEGRADE THE BOUND mRNA?

Transcriptome-wide mRNA stability studies coupled to CLIP-Seq analyses revealed that, surprisingly, TTP does not always cause degradation of the bound target. This has been convincingly demonstrated by employing bone marrow-derived macrophages expressing solely endogenous TTP (9). The study showed that 71% of mRNAs bound by TTP in their 3’ UTR are stable. A similar conclusion was drawn from CLIP-Seq and mRNA stability assays in HEK293 cells overexpressing TTP (92). These observations were supported by other CLIP-Seq studies employing primary cells (i.e. cells not overexpressing TTP) although the evidence was indirect as it was based on differential expression analysis (RNA-Seq) but not on transcriptome-wide mRNA stability assessments (66, 67). These unexpected results indicate that a more complex model of TTP action needs to be developed. The model will probably involve proteins acting in cis with TTP which prevent recruitment of the RNA degradation machinery to stable transcripts or facilitate such recruitment to unstable transcripts (Figure 2). This new concept could also involve yet uncharacterized TTP phosphorylation events; in this scenario a particular phosphorylation (activating or inactivating) would occur only on certain target mRNAs and/or subcellular locations. The advanced concept of TTP function might also consider a recently reported hypothesis that TTP stabilizes mRNA under certain circumstances: The dramatic induction of TTP following an inflammatory stimulus was proposed to generate a pool of free TTP that sequesters the RNA degradation machinery thereby preventing mRNA decay, but a direct evidence for this hypothesis was not provided (93).

Related to the question of whether TTP destabilizes or not a specific subset of bound mRNAs are ribosome profiling data showing that TTP can affect mRNA stability but also inhibit translation (65–67). Particularly conclusive were studies
employing primary macrophages and T cells, i.e. experimental systems expressing solely endogenous and naturally regulated TTP (66, 67). All these studies revealed transcript-selective effects of TTP on translation: some TTP target mRNAs were less abundant at polysomes while others were not depleted from polysomes. Negative regulation of translation has been also implicated in control of inflammatory gene expression in tumor-associated macrophages (94). All these data are consistent with an updated model of TTP function in which cis-acting and transcript-specific RBPsd determine the final consequence of TTP binding to the target mRNA (Figure 2). This updated model is supported by the finding that TTP binds to the cytoplasmic poly(A)-binding protein and that such interactions are required for inhibition of translation by TTP in primary macrophages (67). The model will become more complex once data on tissue/cell type-specific functions of TTP are included. First data on biologically relevant cell type-specific effects of TTP have only recently become available: The mRNA coding for the IL-1β cytokine (Il1b mRNA) is destabilized by TTP in bone marrow-derived dendritic cells but not in bone marrow-derived macrophages despite strong binding to TTP (53). The regulation of Il1b expression by TTP is important in vivo as TTP-deficient mice show higher Il1b mRNA levels in several tissues. Moreover, genetic inactivation of IL-1 signaling in TTP-deficient animals ameliorates the TTP deficiency syndrome (53).

The extent of cell type-specific regulation of TTP activity can be indirectly estimated from a number of RNA-seq studies comparing mRNA levels in wild-type versus TTP knockout cells. For example, the levels of Tnf mRNA, the bona fide TTP target, are comparable in wild-type and TTP-deficient T cells, suggesting that TTP does not target Tnf mRNA for degradation in T cells in contrast to most other cell types (66). Similarly, Il6 mRNA, which is known to be bound and destabilized by TTP in bone marrow-derived macrophages (BMDMs) (55), is more highly expressed also in TTP-deficient dendritic cells (upon 3 h or 6 h LPS stimulation) and T cells (upon 4 h activation) but not in peritoneal neutrophils (53, 60). Reported RNA-seq expression data for selected TTP targets in primary immune cells (BMDMs, BMDCs, peritoneal neutrophils and T cells) from wild-type and TTP-deficient mice are summarized in Table 1. These data convincingly visualize that a comparison of mRNA levels does not provide a definitive information about the destabilization of a particular mRNA by TTP since indirect

![Figure 2](https://example.com/figure2.png) Model of functional and silent binding of TTP to mRNA. Model of possible mechanisms explaining how mRNA-bound TTP destabilizes some mRNAs but not others.
TABLE 1 | Expression data (FPKMs or counts) of selected TTP targets in different immune cell types from wild type and TTP-KO mice.

| Gene_ID | Gene_name | BMDM, 3 h LPS, FPKM | BMDM, 6 h LPS, FPKM | BMDC, 3 h LPS, FPKM | BMDC, 6 h LPS, FPKM | Peritoneal neutrophils, 4 h LPS, FPKM | T cells, 4 h activation, counts | T cells, 3 day activation, counts |
|---------|-----------|---------------------|---------------------|---------------------|---------------------|-------------------------------|-------------------------------|-------------------------------|
| EnSMUSG00000029378 | Areg | ND | ND | ND | ND | 3.93 | 9.12 | 0.17 | 0.88 |
| EnSMUSG00000018930 | Ccl4 | 9008.07 | 10206.05 | 4422.39 | 6764.60 | 652.02 | 1358.16 | 234.16 | 971.93 |
| EnSMUSG00000029380 | Cxcl1 | 629.10 | 1589.36 | 24.27 | 443.73 | 309.38 | 692.45 | 127.96 | 374.72 |
| EnSMUSG00000034855 | Cxcl10 | 11244.27 | 10914.54 | 10272.14 | 9763.24 | 494.36 | 1296.76 | 435.80 | 1888.26 |
| EnSMUSG00000058427 | Cxcl2 | 1563.82 | 5658.09 | 179.03 | 3428.48 | 862.66 | 3066.80 | 325.44 | 2415.03 |
| EnSMUSG00000029379 | Cxcl3 | 384.68 | 351.67 | 35.31 | 230.81 | 948.92 | 1404.63 | 536.80 | 1536.96 |
| EnSMUSG00000003541 | Ier3 | 173.04 | 335.38 | 215.25 | 358.83 | 27.72 | 69.97 | 31.33 | 77.18 |
| EnSMUSG00000016529 | Il10 | 71.76 | 171.35 | 129.47 | 680.55 | 0.67 | 5.57 | 0.22 | 2.99 |
| EnSMUSG00000027399 | Il1a | 32.43 | 60.61 | 13.80 | 28.18 | 286.92 | 737.09 | 173.03 | 547.67 |
| EnSMUSG00000027398 | Il1b | 138.34 | 150.00 | 70.07 | 82.29 | 412.66 | 1241.13 | 259.85 | 940.15 |
| EnSMUSG00000025746 | Il6 | 72.51 | 62.09 | 35.80 | 76.62 | 293.93 | 629.44 | 317.59 | 684.42 |
| EnSMUSG00000032487 | Ptgs2 (or Cox2) | 206.85 | 155.98 | 1396.01 | 1288.74 | 1.09 | 3.96 | 3.14 | 12.91 |
| EnSMUSG00000020826 | Nos2 | 309.54 | 357.49 | 469.67 | 849.94 | 79.64 | 165.24 | 44.39 | 130.91 |
| EnSMUSG00000038037 | Socs1 | 487.62 | 538.13 | 159.49 | 206.37 | 60.32 | 124.91 | 55.28 | 208.53 |
| EnSMUSG00000053113 | Socs3 | 484.52 | 585.97 | 417.63 | 455.86 | 67.84 | 87.22 | 39.03 | 67.06 |
| EnSMUSG00000024401 | Tnf | 321.7 | 480.01 | 509.77 | 6261.88 | 522.33 | 1937.24 | 163.15 | 1186.23 |

BMDM, bone marrow-derived macrophages.
BMDC, bone marrow-derived dendritic cells.
ND, not determined (too low expression).

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OUTLOOK

Despite more than 25 years of research, TTP continues to represent an important and fruitful model for studies on RBPs and cell-type specific functions of TTP to answer the still incompletely understood phenotype of TTP X. While an in-depth analysis of TTP-containing protein complexes and yet uncharacterized phosphorylation sites mechanically poorly defined, and thus offering a unique opportunity to characterize the regulation of mRNA in general and the regulation of immune responses in particular. Technological progress in recent years and advanced animal models were instrumental for the identification of novel regulatory facets and functional consequences of TTP which fundamentally improved our understanding of physiological and pathological mRNA decay in therapy of inflammatory diseases and cancer.

In summary, these findings imply that cell-type specific RNA-binding proteins act together with TTP to stabilize or destabilize select TTP targets. Comprehensive biochemical studies including purification of TTP-associated protein complexes and yet uncharacterized phosphorylation sites are needed to precisely determine the regulatory facets and functional consequences of TTP which are relevant for the entire TTP family, as the functional relevance of TTP silence in vivo is important by itself or in combination with other TTP targets.

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AUTHOR CONTRIBUTIONS

PK designed the concept and wrote the manuscript. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Turner M, Diaz-Munoz MD. RNA-Binding Proteins Control Gene Expression and Cell Fate in the Immune System. *Nat Immunol* (2018) 19:1203–12. doi: 10.1038/s41591-017-0028-4

2. Akira S, Maeda K. Control of RNA Stability in Immunity. *Annu Rev Immunol* (2013) 31:491–509. doi: 10.1146/annurev-immunol-101810-115714

3. Carpenter S, Ricci EP, Mercier BC, Moore MJ, Fitzgerald KA. Post-transcriptional Regulation of Gene Expression in Innate Immune *Nat Rev* (2014) 14:361–76. doi: 10.1038/nri3682

4. Shaw G, Kamen R. A Conserved AU Sequence From the 3′ Untranslated Region of GM-CSF mRNA Mediates Selective mRNA Degradation. *Cell* (1986) 46:659–67. doi: 10.1016/0092-8674(86)90341-7

5. Kontoyiannis D, Paparaskas M, Pizarro TT, Cominelli F, Kollas G. Impaired off/On Regulation of TNF Biosynthesis in Mice Lacking TNF AU-Rich Elements: Implications for Joint and Gut-Associated Immunopathologies. *Immunity* (1999) 10:387–98. doi: 10.1016/S1074-7613(00)80538-2

6. Yang E, van Nimwegen E, Zavolan M, Rajewsky N, Schroeder M, Magnasco M, et al. Decay Rates of Human mRNAs: Correlation With Functional Characteristics and Sequence Attributes. *Genome Res* (2003) 13:1863–72. doi: 10.1101/gr.1272403

7. Bakheet T, Hitti E, Al-Saif M, Moghrabi WN, Khabar KSA. The AU-Rich Element Landscape Across Human Transcriptome Reveals a Large Proportion In Introns and Regulation by ELAVL1/HuR. *Biochim Biophys Acta Gene Regul Mech* (2018) 1861:167–77. doi: 10.1016/j.bbagrm.2017.12.006

8. Hao S, Baltimore D. The Stability of mRNA Influences the Temporal Order of the Induction of Genes Encoding Influenzaviruses. *Nat Med* (2009) 15:281–8. doi: 10.1038/nm.1699

9. Sedlyarov V, Fallmann J, Ebner F, Huemer J, Sneezum L, Ivin M, et al. Tristetraprolin Binding Site Atlas in the Macrophage Transcriptome Reveals a Switch for Inflammation Resolution. *Mol Syst Biol* (2016) 12:868. doi: 10.15252/msb.20156628

10. Diaz-Munoz MD, Turner M. Uncovering the Role of RNA-Binding Proteins in Gene Expression in the Immune System. *Front Immunol* (2018) 9:1094. doi: 10.3389/fimmu.2018.01194

11. Yoshinaga M, Takeuchi O, RNA-Binding Proteins in the Control of Autoimmune Diseases. *Immunol Med* (2019) 42:53–64. doi: 10.1080/25788526.2019.1655192

12. Labno A, Tomecki R, Dziembowski A. Cytoplasmic RNA Decay Pathways - Enzymes and Mechanisms. *Biochim Biophys Acta* (2016) 1863:3125–47. doi: 10.1016/j.bbamcr.2016.09.023

13. Zinder JC, Lima CD. Targeting RNA for Processing or Destruction by the Eukaryotic RNA Exosome and its Cofactors. *Genes Dev* (2017) 31:88–100. doi: 10.1101/gad.294769.116

14. Uehata T, Iwasaki H, Vandenbon A, Matsushita K, Hernandez-Cuellar E, et al. RNA-Binding Proteins ZFP36L1 and ZFP36L2 Promote Cell Quiescence. *Science* (2016) 352:453–9. doi: 10.1126/science.aad5978

15. Lu JY, Sadri N, Schneider RJ. Endotoxic Shock in AUFI Knockout Mice Mediated by Failure to Degrade Proinflammatory Cytokine mRNAs. *Genes Dev* (2006) 20:3174–84. doi: 10.1101/gad.1467606

16. Grudzien-Nogalska E, Kiledjian M. New Insights Into Decapping Enzymes Expression. *Nat Immunol* (2010) 11:717–24. doi: 10.1038/ni.1901

17. Collart MA. The Ccr4-Not Complex is a Key Regulator of Eukaryotic Gene Expression. *EMBO J* (2000) 19:4311–20. doi: 10.1093/emboj/19.6.4311

18. Pont AR, Sadri N, Hsiao SJ, Smith S, Schneider RJ. mRNA Decay Factor AUFI Maintains Normal Aging, Telomere Maintenance, and Suppression of Senescence by Activation of Telomerase Transcription. *Mol Cell* (2012) 47:5–15. doi: 10.1016/j.molcel.2011.04.019

19. Chen J, Cagiao J, Magee JD, Techasantana P, Cubin MM, Damh GM, et al. Posttranscriptional Gene Regulation of IL-17 by the RNA-Binding Protein HuR Is Required for Initiation of Experimental Autoimmune Encephalomyelitis. *J Immunol* (2013) 191:5441–50. doi: 10.4049/jimmunol.1301188

20. Akira S, De Maria CT, Sun Y, Wilson GM, Brewer G. Structure and Function of the RNA-Binding Protein HuR. *Cell* (2004) 24:657–9. doi: 10.1038/ncomms6248

21. Yoon JH, De S, Srikantan S, Abdelmohsen K, Grammatikakis I, Kim J, et al. PAR-CLIP Analysis Uncovers AUFI Impact on Target RNA Fate and Lipid Homeostasis in Response to High-Fat Diet. *Nat Commun* (2020) 11:3067. doi: 10.1038/s41467-020-16918-x

22. Katsanou V, Milatos S, Yiakougkavi S, Gantzis N, Kotsoni A, Alexiou M, et al. The RNA-Binding Protein Elav1/HuR Is Essential for Placental Branching Morphogenesis and Embryonic Development. *Mol Cell Biol* (2009) 29:2762–76. doi: 10.1128/MCB.01393-08

23. Lang M, Berry D, Passercek K, Mesteri I, Bhuji S, Ebner F, et al. HuR Small-Molecule Inhibitor Elicits Differential Effects in Adenomatosis Polyposis Coli and Colorectal Carcinogenesis. *Cancer Res* (2017) 77:2424–38. doi: 10.1158/0008-5472.CAN-15-1726

24. Wells ML, Perera L, Blackshear PJ. An Ancient Family of RNA-Binding Proteins: Still Important! *Trends Biochem Sci* (2017) 42(4):285–96. doi: 10.1016/j.tibs.2016.12.003

25. Tan D, Zhou M, Kiledjian M, Tong L. The ROQ Domain of Roquin Recognizes mRNA Constitutive-Decay Element and Double-Stranded RNA. *Nat Struct Mol Biol* (2011) 18:679–85. doi: 10.1038/nsmb.2085

26. Yokogawa M, Tushima T, Noda NN, Kuma H, Enokizono Y, Yamashita K, et al. Disruption of Zfp36L1, a Gene Encoding a CCCH Tandem Zinc Finger Protein, Results in Defective Hematopoiesis. *Dev Genet* (2014) 14:361. doi: 10.1073/pnas.1307419110

27. Wagner BJ, DeMaria CT, Sun Y, Wilson GM, Brewer G. Structure and Function of the RNA-Binding Protein HuR. *Cell* (2004) 24:657–9. doi: 10.1038/ncomms6248

28. Stumpo DJ, Byrd NA, Phillips RS, Ghosh S, Maronpot RR, Castranio T, et al. Chioroalloctino Fusion Defects and Embryonic Lethality Resulting From Disruption of Zfp36L1, a Gene Encoding a CCCH Tandem Zinc Finger Protein of the Tristetraprolin Family. *Mol Cell Biol* (2004) 24:6445–55. doi: 10.1128/MCB.24.14.6445-6455.2004

29. Stumpo DJ, Broxmeyer HE, Ward T, Cooper S, Hangoc G, Chung YJ, et al. Targeted Disruption of Zfp36l2, Encoding a CCCH Tandem Zinc Finger RNA-Binding Protein, Results in Defective Hematopoiesis. *Blood* (2009) 114:2401–10. doi: 10.1182/blood-2009-04-214619

30. Lebedeva S, Jens M, Then K, Schwanhauser B, Selbach M, Landthaler M, et al. Transcripome-Wide Analysis of Regulatory Interactions of the RNA-Binding Protein HuR. *Mol Cell* (2011) 43:430–52. doi: 10.1016/j.molcel.2011.06.008
40. Mukherjee N, Corcoran DL, Nusbaum JD, Reid DW, Georgiev S, Hafner M, et al. Integrative Regulatory Mapping Indicates That the RNA-Binding Protein HuK Couples pre-mRNA Processing and mRNA Stability. *Mol Cell* (2011) 43:327–39. doi: 10.1016/j.molcel.2011.06.007

41. Leppke K, Schott J, Reitter S, Poetz F, Hammond MC, Stecklein G. Roquin Promotes Constitutive mRNA Decay via a Conserved Class of Stem-Loop Recognition Motifs. *Cell* (2013) 153:869–81. doi: 10.1016/j.cell.2013.04.016

42. Mino T, Murakawa Y, Fukao A, Tasciani S, Ivin M, Kratovilich F, Gratz N, et al. The RNA-Binding Protein Tristetraprolin Triggers Apoptosis of Pathogen-Engaged Neutrophils During Bacterial Infection. *J Clin Invest* (2017) 127:2051–65. doi: 10.1172/JCI86311

43. Chang SH, Elmento O, Zhang J, Zhuang ZW, Simons M, Hla T. ELAV1 Regulates Alternative Splicing of Eif4e Transporter to Promote Postnatal Angiogenesis. *Proc Natl Acad Sci USA* (2014) 111:18309–14. doi: 10.1073/pnas.1412177111

44. Blackshear PJ, Perera L. Phylogenetic Distribution and Evolution of the TRISTETRAPROLIN Family. *PLoS Genet* (2011) 7:560. doi: 10.1371/journal.pgen.1001147

45. Puig S, Askeland E, Thiele DJ. Coordinated Remodeling of Cellular mRNA Decay in Influenza A Virus-Infected Cells. *Nucleic Acids Res* (2011) 39:4373–86. doi: 10.1093/nar/gkr011

46. Taylor GA, Carballo E, Lee DM, Lai WS, Thompson MJ, Patel DD, et al. A Natural RNA Circles Function as Effector Molecules in T Cell Activation. *Cell* (2018) 173:1093–109. doi: 10.1016/j.cell.2018.03.029

47. Brewer BY, Malicka J, Blackshear PJ, Wilson GM. RNA Sequence Elements Required for High Affinity Binding by the Zinc Finger Domain of Tristetraprolin: Conformational Changes Coupled to the Bipartite Nature of AU-Rich RNA-Destabilizing Motifs. *J Biol Chem* (2004) 279:27870–7. doi: 10.1074/jbc.M402551200

48. Tiedje C, Diaz-Munoz MD, Trulley P, Ahlfors H, Laass K, Blackshear PJ, et al. The RNA-Binding Protein TTP is a Global Post-Transcriptional Regulator of Feedback Control in Inflammation. *Nucleic Acids Res* (2016) 44:7418–40. doi: 10.1093/nar/gkw474

49. Fabian MR, Frank F, Rouya C, Siddiqui N, Lai WS, Karetinkov A, et al. Structural Basis for the Recruitment of the Human CCR4-NOT Deadenylase Complex by Tristetraprolin. *Nat Struct Mol Biol* (2013) 20:735–9. doi: 10.1038/nsmb.2572

50. Taylor GA, Carballo E, Lai WS, Blackshear PJ. Feedback Inhibition of Macrophage Tumor Necrosis Factor-α Production by Keratinocytes Controls Local and Systemic Inflammatory Responses by Induction of Tristetraprolin. *J Exp Med* (2017) 214:6023–34. doi: 10.1084/jem.20160912

51. Ebner F, Sedlyarov V, Tasciani S, Ivin M, Kratovilich F, Gratz N, et al. The RNA-Binding Protein Tristetraprolin Triggers Apoptosis of Pathogen-Engaged Neutrophils During Bacterial Infection. *J Clin Invest* (2017) 127:2051–65. doi: 10.1172/JCI86311

52. Brewer BY, Malicka J, Blackshear PJ, Wilson GM. RNA Sequence Elements Required for High Affinity Binding by the Zinc Finger Domain of Tristetraprolin: Conformational Changes Coupled to the Bipartite Nature of AU-Rich RNA-Destabilizing Motifs. *J Biol Chem* (2004) 279:27870–7. doi: 10.1074/jbc.M402551200

53. Stecklein G, Tendenbaum SA, Mayo T, Chittur SV, George AD, Baron TJ, et al. Genome-Wide Analysis Identifies Interleukin-10 mRNA as Target of Tristetraprolin. *J Biol Chem* (2008) 283:11689–99. doi: 10.1074/jbc.M709675200

54. Mecszczak S, Jens M, Elefsinioti A, Torti F, Krueger J, Rybak A, et al. Circular RNAs Are A Large Class of Animal RNAs With Regulatory Potency. *Nature* (2013) 495(7441):333–8. doi: 10.1038/nature12192

55. Hansen TB, Jensen TI, Clausen BH, Bramsen JB, Finsen B, Damgaard CK, et al. Natural RNA Circles Function as Efficient microRNA Sponges. *Nature* (2013) 495(7441):38–4. doi: 10.1038/nature12193

56. Sander H, Stecklein G. Control of mRNA Decay by Phosphorylation of Tristetraprolin. *Biochem Soc Trans* (2008) 36:491–6. doi: 10.1042/BST0360491

57. Kovarik et al. Control of Inflammation by TTP
81. Tchen CR, Brook M, Saklatvala J, Clark AR. The Stability of Tristetraprolin mRNA is Regulated by Mitogen-Activated Protein Kinase P38 and by Tristetraprolin Itself. J Biol Chem (2004) 279:32393–400. doi: 10.1074/jbc.M402095200

82. Brook M, Tchen CR, Santalucia T, Mellrath J, Arthur JS, Saklatvala J, et al. Posttranslational Regulation of Tristetraprolin Subcellular Localization and Protein Stability by P38 Mitogen-Activated Protein Kinase and Extracellular Signal-Regulated Kinase Pathways. Mol Cell Biol (2006) 26:2408–18. doi: 10.1128/MCB.26.6.2408-2418.2006

83. Ngoc LV, Wauquier C, Soin R, Bousbata S, Twyffels L, Kruys V, et al. Rapid Proteasomal Degradation of Posttranscriptional Regulators of the TIS11/tristetraprolin Family is Induced by an Intrinsically Unstructured Region Independently of Ubiquitination. Mol Cell Biol (2014) 34:4315–28. doi: 10.1128/MCB.00643-14

84. Hitti E, Lakovleva T, Brook M, Deppenmeier S, Gruber AD, Radtch D, et al. Mitogen-Activated Protein Kinase-Activated Protein Kinase 2 Regulates Tumor Necrosis Factor mRNA Stability and Translation Mainly by Altering Tristetraprolin Expression, Stability, and Binding to Adenine/Uridine-Rich Element. Mol Cell Biol (2006) 26:2399–407. doi: 10.1128/MCB.26.6.2399-2407.2006

85. Clement SL, Scheckel C, Stoecklin G, Lykke-Andersen J. Phosphorylation of Tristetraprolin by MK2 Impairs AU-Rich Element mRNA Decay by Preventing Deadenylase Recruitment. Mol Cell Biol (2011) 31:256–66. doi: 10.1128/MCB.00717-10

86. Stoecklin G, Stubbs T, Kedersha N, Wax S, Rigby WF, Blackwell TK, et al. MK2-Induced Tristetraprolin:14-3-3 Complexes Prevent Stress Granule Association and ARE-mRNA Decay. EMBO J (2004) 23:1313–24. doi: 10.1038/sj.emboj.7600163

87. Johnson BA, Blackwell TK. Multiple Tristetraprolin Sequence Domains Required to Induce Apoptosis and Modulate Responses to TNFalpha Through Distinct Pathways. Oncogene (2002) 21:4237–46. doi: 10.1038/sj.onc.1205526

88. Tiedje C, Ronkina N, Tehrani M, Dhamija S, Laass K, Holtmann H, et al. The P38/MK2-Driven Exchange Between Tristetraprolin and HuR Regulates AU-Rich Element-Dependent Translation. PloS Genet (2012) 8:e1002977. doi: 10.1371/journal.pgen.1002977

89. Ross EA, Smallie T, Ding Q, O’Neill JD, Cunliffe HE, Tang T, et al. Dominant Suppression of Inflammation via Targeted Mutation of the mRNA Destabilizing Protein Tristetraprolin. J Immunol (2015) 195:265–76. doi: 10.4049/jimmunol.1402826

90. Clark AR, Dean JL. The Control of Inflammation via the Phosphorylation and Dephosphorylation of Tristetraprolin: A Tale of Two Phosphatases. Biochem Soc Trans (2016) 44:1321–37. doi: 10.1042/BST20160166

91. Ronkina N, Shushakova N, Tiedje C, Yakovleva T, Tollenare MAX, Scott A, et al. The Role of TTP Phosphorylation in the Regulation of Inflammatory Cytokine Production by MK2/3. J Immunol (2019) 203:2291–300. doi: 10.4049/jimmunol.1801221

92. Mukherjee N, Jacobs NC, Hafner M, Kennington EA, Nusbaum JD, Tuschl T, et al. Global Target mRNA Specification and Regulation by the RNA-Binding Protein ZFP36. Genome Biol (2014) 15:R12. doi: 10.1186/gb-2014-15-1-r12

93. Mahmoud L, Moghrabi W, Khabar KSA, Hitti EG. Bi-Phased Regulation of Tristetraprolin Family is Induced by an Intrinsically Unstructured Region Independently of Ubiquitination. RNA Biol (2015) 12:3054–64. doi: 10.1186/s12251-015-0453-1

94. Kratochvill F, Gratz N, Qualls JE, Van De Velde LA, Chi H, Kovarik P, et al. Tristetraprolin Limits Inflammatory Cytokine Production in Tumor-Associated Macrophages in an mRNA Decay-Independent Manner. Cancer Res (2015) 75:3054–64. doi: 10.1158/0008-5472.CAN-15-0205

95. Salerno F, Engels S, van den Biggelaar M, van Alphen FPJ, Guislain A, Zhao W, et al. Translational Repression of Pre-Formed Cytokine-Encoding mRNA Prevents Chronic Activation of Memory T Cells. Nat Immunol (2018) 19 (8):828–37. doi: 10.1038/s41590-018-0155-6

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