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The p38 MAPK pathway inhibits tristetraprolin-directed decay of interleukin-10 and pro-inflammatory mediator mRNAs in murine macrophages

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ABSTRACT

p38 mitogen-activated protein kinase (MAPK) stabilises pro-inflammatory mediator mRNAs by inhibiting AU-rich element (ARE)-mediated decay. We show that in bone-marrow derived murine macrophages tristetraprolin (TTP) is necessary for the p38 MAPK-sensitive decay of several pro-inflammatory mRNAs, including cyclooxygenase-2 and the novel targets interleukin (IL)-6, and IL-1α. TTP$^{-/-}$ macrophages also strongly overexpress IL-10, an anti-inflammatory cytokine that constrains the production of the IL-6 despite its disregulation at the post-transcriptional level. TTP directly controls IL-10 mRNA stability, which is increased and insensitive to inhibition of p38 MAPK in TTP$^{-/-}$ macrophages. Furthermore, TTP enhances deadenylation of an IL-10 3′-untranslated region RNA in vitro.

1. Introduction

The presence of an AU-rich element (ARE) in the 3′-untranslated region (UTR) of a large number of mRNAs causes them to be highly unstable. Many ARE-containing mRNAs of the inflammatory response are stabilised following activation of p38 mitogen-activated protein kinase (MAPK) [1]. Tristetraprolin (TTP) regulates the expression of tumour necrosis factor (TNF) by binding the ARE in the 3′UTR of TNF mRNA and targeting it for degradation [2]. TTP knockout mice develop a complex inflammatory phenotype and display inflammatory arthritis, cachexia, conjunctivitis and myeloid hyperplasia caused by increased TNF production [3]. TTP also regulates granulocyte-macrophage colony-stimulating factor [4], interleukin (IL)-2 [5], immediate-early response gene 3 [6], IL-10 [7] and chemokine (C-X-C) ligand 1 (CXCL1) [8] mRNA stability.

Circumstantial evidence suggests that the p38 MAPK pathway regulates mRNA stability by inactivating TTP. TTP promotes mRNA deadenylation [4,9], whereas p38 MAPK inhibits it [10] and TTP is a substrate of the kinase downstream of p38 MAPK, MAPK-activated protein kinase 2 (MK2) [11]. Blockade of TNF biosynthesis by p38 MAPK inhibition was shown to be impaired in TTP$^{-/-}$ cells [12]. More directly, it was shown that post-transcriptional regulation of TNF [13] and CXCL1 [8] expression by the p38 MAPK pathway is TTP-dependent. However, other RNA-binding proteins such as HuR and KSRP have also been implicated as mediators of post-transcriptional responses to p38 MAPK [1,14]. It is therefore unclear to what extent TTP is responsible for post-transcriptional effects of p38 MAPK during an inflammatory response. To answer this question we investigated post-transcriptional regulation of several mediators of the inflammatory response in wild-type and TTP$^{-/-}$ macrophages stimulated with lipopolysaccharide (LPS).

2. Materials and methods

2.1. Materials

4-(4-Fluorophenyl)-2-(4-hydroxyphenyl)-5-(4-pyridyl)1H-imidazole (SB 202190), LPS (*Salmonella typhimurium*) and [α-^{32}P]-UTP were from Calbiochem-Novabiochem, Sigma–Aldrich and GE

Abbreviations: MAPK, mitogen-activated protein kinase; TTP, tristetraprolin; IL, interleukin; ARE, AU-rich element; UTR, untranslated region; TNF, tumour necrosis factor; CXCL1, chemokine (C-X-C motif) ligand 1; BMDM, bone marrow-derived macrophages; LPS, lipopolysaccharide; FCS, foetal calf serum; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; GST, glutathione-*S*-transferase; Act D, actinomycin D

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Healthcare, respectively. Anti-IL-10, anti-COX-2 and anti-α-tubulin antibodies were from R&D systems, Alexis and Sigma–Aldrich respectively. Details of riboprobe templates and IL-10 3′UTR in vitro deadenylation assay and BBB IL-10 3′UTR plasmids are available upon request.

2.2. Mice

TTP$^{-/-}$ mice were originally generated previously [3]. TTP$^{-/-}$ mice were of mixed 129 and C57BL/6 background as originally obtained from Perry Blackshear. All animal experiments were performed according to ethical procedures.

2.3. Bone marrow-derived macrophage (BMDM) preparation

TTP$^{-/-}$ and wild-type littermate mice were humanely culled and bone marrow was extracted. Macrophages were derived by differentiation with L929-cell conditioned medium or macrophage colony stimulating factor (PeproTech) [13].

2.4. mRNA measurements

Total RNA was isolated from BMDM using a QIAamp kit (Qiagen). TNF, cyclooxygenase-2 (COX-2) and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) mRNAs were analysed by northern blotting as described previously [10]. IL-10 (and GAPDH) mRNA was measured by quantitative RT-PCR (see Supplementary data for details). Other endogenous mRNAs were quantified using a ribonuclease protection assay kit and mCK-2b template set (BD Biosciences). Analysis of reporter mRNA stability was performed by ribonuclease protection assay as described previously [10].

2.5. Enzyme-linked immunosorbent assay (ELISA) and Western blotting

ELISAs for IL-6 and TNF (R&D systems), IL-10 (BD Biosciences), IL12p40 (EBioscience) were performed according to the manufacturer's instructions. Western blotting was performed according to standard procedures.

2.6. Electrophoretic mobility shift assay

An RNA oligonucleotide spanning the IL-1α ARE was synthesised commercially (Dharmacon). The sequence was: GUUAUUUUUAAGUUAUUUAUCUAUGUAUUUAUAAUAUAUUUAUGAUAAUUAUAUUAUUUAUG. The oligonucleotide was end-labelled with [γ-^{32}P]ATP (3000 Ci/mmol) using T4 polynucleotide kinase. ^{32}P-labelled RNA probe (approx. 0.1 pmol) was incubated for 15 min at room temperature with 100 ng of GST–TTP or glutathione-*S*-transferase (GST) in the absence or presence of a 10-fold excess (1 pmol) of unlabelled IL-1α or antisense β-globin riboprobe in 20 μl of bandshift buffer (20 mM HEPES, pH 7.2, 100 μM $ZnCl_2$, 50 mM KCl, 1 mM DTT, 5% glycerol) containing heparin sulfate (5 mg/ml). Unlabelled antisense β-globin riboprobe [4] was prepared by in vitro transcription by standard methods and quantified by Nanodrop. Two microlitres of loading buffer (80% glycerol, 0.1% bromophenol blue) was then added and RNA–protein complexes were resolved by electrophoresis on a 4% (w/v) acrylamide/Tris–borate gel using Tris–borate running buffer. Complexes were visualised using a phosphorimager (FLA5000; Fuji). The image shown was gamma corrected to improve the contrast in order to visualise complexes more clearly.

2.7. In vitro deadenylation assay

This was performed similarly to Lai et al. [9] (see Supplementary data).

3. Results

3.1. p38 MAPK stabilises mRNAs of the inflammatory response by inactivation of TTP

To investigate whether p38 MAPK-mediated inhibition of TTP-directed decay represents a more general mechanism than that currently suggested [8,13], the stability of several p38 MAPK-regulated mRNAs was examined by actinomycin (Act) D chase in LPS-treated wild-type and TTP$^{-/-}$ bone marrow-derived macrophages (BMDM) in the presence or absence of p38 MAPK blockade. IL-10 mRNA was also examined as it contains an ARE and is a recently identified TTP target [7]. In wild-type cells there was little decay of IL-10, COX-2, IL-6, and IL-1α mRNAs in the absence of SB 202190 (Fig. 1 and Table 1) but addition of the inhibitor resulted in their rapid destabilisation (Fig. 1 and Table 1). The inhibitor had no effect on the stability of these mRNAs in TTP$^{-/-}$ BMDM (Fig. 1 and Table 1). Similar results were obtained for TNF mRNA (Table 1). This was independently confirmed by pre-treatment of cells with SB 202190 1 h prior to LPS stimulation (to block TTP expression) for 4 h followed by actinomycin D (Act D) chase or by simultaneously adding the inhibitor with Act D (Fig. 1I).

In LPS-treated TTP$^{-/-}$ cells in the absence of SB 202190 the stability of IL-10 mRNA was 2.5-fold greater than in wild-type cells (Fig. 1 and Table 1), confirming it as a TTP target [7]. SB 202190 displays relatively good specificity at the 1 μM concentration used (Fig. 1A–H). Nevertheless, the novel p38 MAPK-mediated stabilisation of IL-10 mRNA was confirmed using a tetracycline-regulated reporter system [10] (Fig. 2). Active mutants of MKK6, a p38 MAPK activator, and MK2 stabilised an IL-10 3′UTR reporter mRNA (Fig 2). IL-12p40, IL-1β, IL-1 receptor antagonist, macrophage inhibitory factor, L32 and GAPDH mRNA half-lives were unaffected by SB202190 treatment in wild-type and TTP$^{-/-}$ BMDM (data not shown). Overall, these results show that p38 MAPK-mediated inhibition of TTP-directed mRNA decay represents a common mechanism for six (including previously published CXCL1 [8]) different mRNAs of the inflammatory response. IL-1α mRNA was shown to be a direct target of TTP by electrophoretic mobility shift assay (Fig. 2E).

3.2. Expression of inflammatory response mRNAs and proteins in wild-type and TTP$^{-/-}$ BMDM

To investigate whether TTP regulates the expression of its targets, inflammatory response mRNAs and proteins were measured in unstimulated wild-type and TTP$^{-/-}$ macrophages and at 4 h post-LPS. LPS-treated TTP$^{-/-}$ BMDM expressed ~5-fold more IL-10 mRNA (Fig. 3A) and ~4-fold more protein (Fig. 3B) than wild-type cells. TNF and COX-2 mRNA and protein expression was also upregulated in LPS-treated TTP$^{-/-}$ BMDM (Fig. 3A, B and C) as reported previously [3,15]. Surprisingly, LPS-induced IL-6 mRNA and protein expression was inhibited in TTP$^{-/-}$ cells (Fig. 3A and B). IL-12p40 mRNA and protein expression induced by LPS was also reduced in TTP$^{-/-}$ cells (Fig. 3A and B). IL-1α mRNA was unchanged (Fig. 3A). There was no significant difference in inflammatory mediator expression in unstimulated wild-type and knockout cells. Of the mediators examined, IL-10 was most strongly upregulated in LPS-treated TTP$^{-/-}$ BMDM suggesting an important role for TTP in regulating its expression.

3.3. IL-10 blockade rescues IL-6 and IL-12p40 production in TTP$^{-/-}$ BMDM

Since it could be possible that the reduction in IL-6 and IL-12p40 protein in TTP$^{-/-}$ BMDM is due to increased production of

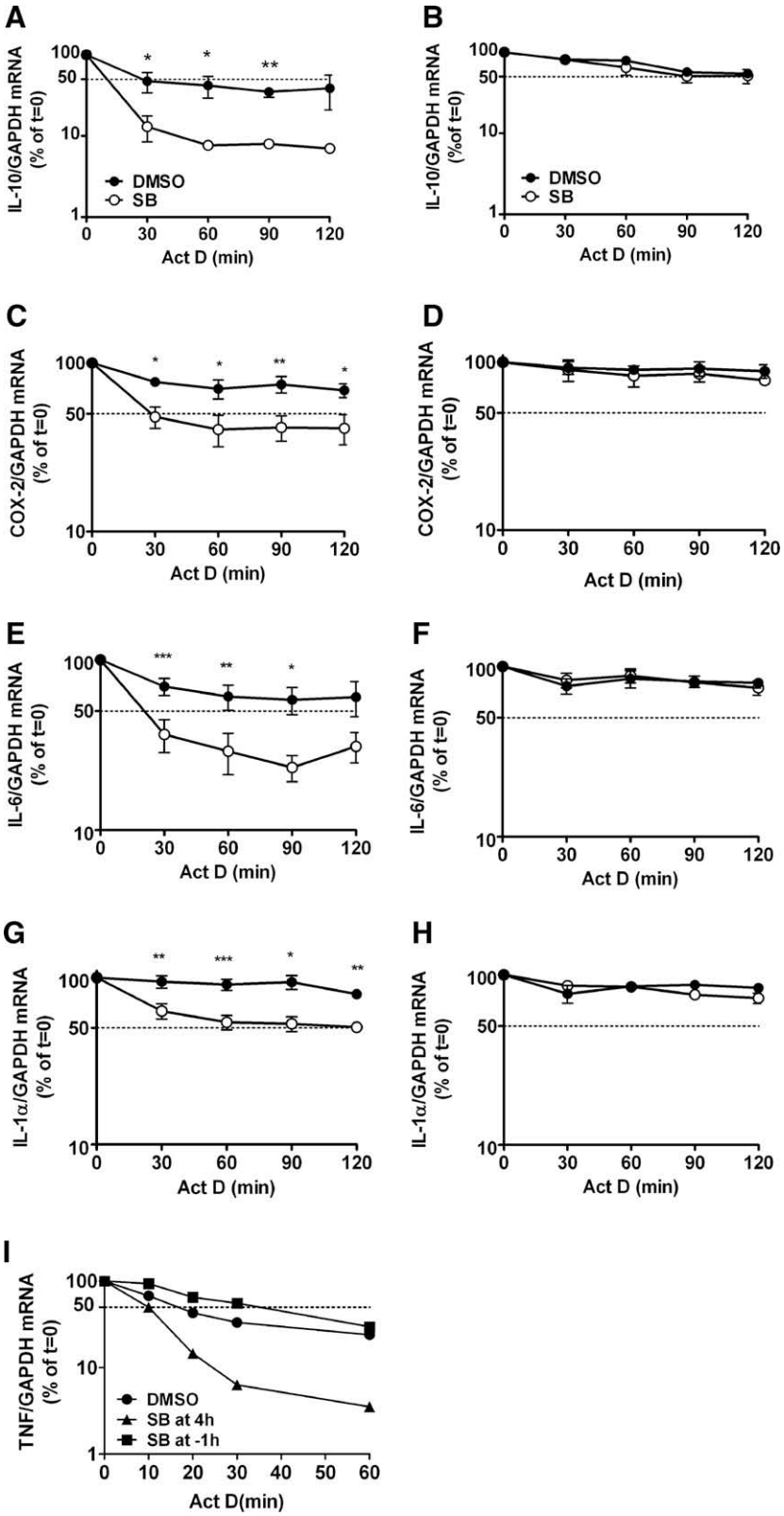

Fig. 1. Regulation of inflammatory response mRNA stability by p38 MAPK requires TTP. Wild-type (A, C, E, G) or $TTP^{-/-}$ (B, D, F, H) BMDM were treated with LPS (10 ng ml^{-1}) for 4 h and then Act D (10 μg ml^{-1}) was added together with SB 202190 (final concentration 1 μM) or vehicle (0.1% DMSO). Cells were harvested at the times shown and RNA isolated and mRNA measured (see materials and methods). Graphs show mean inflammatory response mRNA in wild-type (A, C, E, G) or $TTP^{-/-}$ cells (B, D, F, H) normalised to GAPDH mRNA expressed as a percentage of $t = 0$ Act D treatment ± S.E.M. from at least three independent experiments. Where not shown error bars are smaller than the symbols. Significance was determined by paired Student's t-test $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$. (I) Act D chase for TNF mRNA in wild-type BMDM as above, but with 1 μM SB 202190 added simultaneously with Act D at 4 h, or 5 μM SB 202190 added at 1 h prior to LPS stimulation to block TTP expression. Representative of two independent experiments.

Table 1
Stability of mRNAs in wild-type and TTP$^{-/-}$ BMDM in the presence or absence of p38 MAPK inhibitor. Half-lives ($t_{1/2}$) of initial decay were calculated for $t = 0 - 60$ min post-Act D.

mRNA	Wild-type BMDM		TTP$^{-/-}$ BMDM	
	$t_{1/2(DMSO)}$ (min)	$t_{1/2(SB)}$ (min)	$t_{1/2(DMSO)}$ (min)	$t_{1/2\ (SB)}$ (min)
IL-10	50 ± 16	14 ± 0.3	127 ± 19	111 ± 36
COX-2	128 ± 44	43 ± 8	>300	>300
IL-6	62 ± 12	26 ± 5	301	277
IL-1α	>300	65 ± 15	>300	247
TNF	44 ± 5	15 ± 1	87 ± 5	55 ± 2

IL-10, IL-10 was neutralised with an antibody raised against it. Sixteen hours LPS treatment resulted in a greater difference in TNF expression between wild-type and TTP$^{-/-}$ BMDM (Fig. 3D) compared with 4 h stimulation (Fig. 3B). Pre-treatment of cells with anti-IL-10 prior to LPS increased TNF to a similar degree in the two cell types (Fig 3D). It also increased IL-6 production in wild-type cells, and completely restored IL-6 expression in TTP$^{-/-}$ cells (Fig. 3E). Similar results were obtained for IL-12p40 (Fig. 3F). Thus the reduced expression of IL-6 and IL-12p40 in TTP$^{-/-}$ BMDM can be attributed to increased production of IL-10 arising from TTP deficiency. It is noted that IL-1α mRNA, which is also known to be regulated by IL-10 was inhibited in TTP$^{-/-}$ BMDM at 20 h post-LPS (data not shown).

3.4. TTP directs deadenylation of an IL-10 RNA substrate in vitro

To investigate how TTP regulates IL-10 mRNA decay, an in vitro deadenylation assay was performed using HeLa cell S100, GST–TTP, and ^{32}P-labelled RNA substrates containing portions of the IL-10 3′UTR with poly(A) tails of 100 nucleotides. Three IL-10 RNA substrates were used: nucleotides 601–739 (no AUUUA motifs), 739–920 (5 AUUUAs) and 920–1295 (1 AUUUA motif) of the IL-10

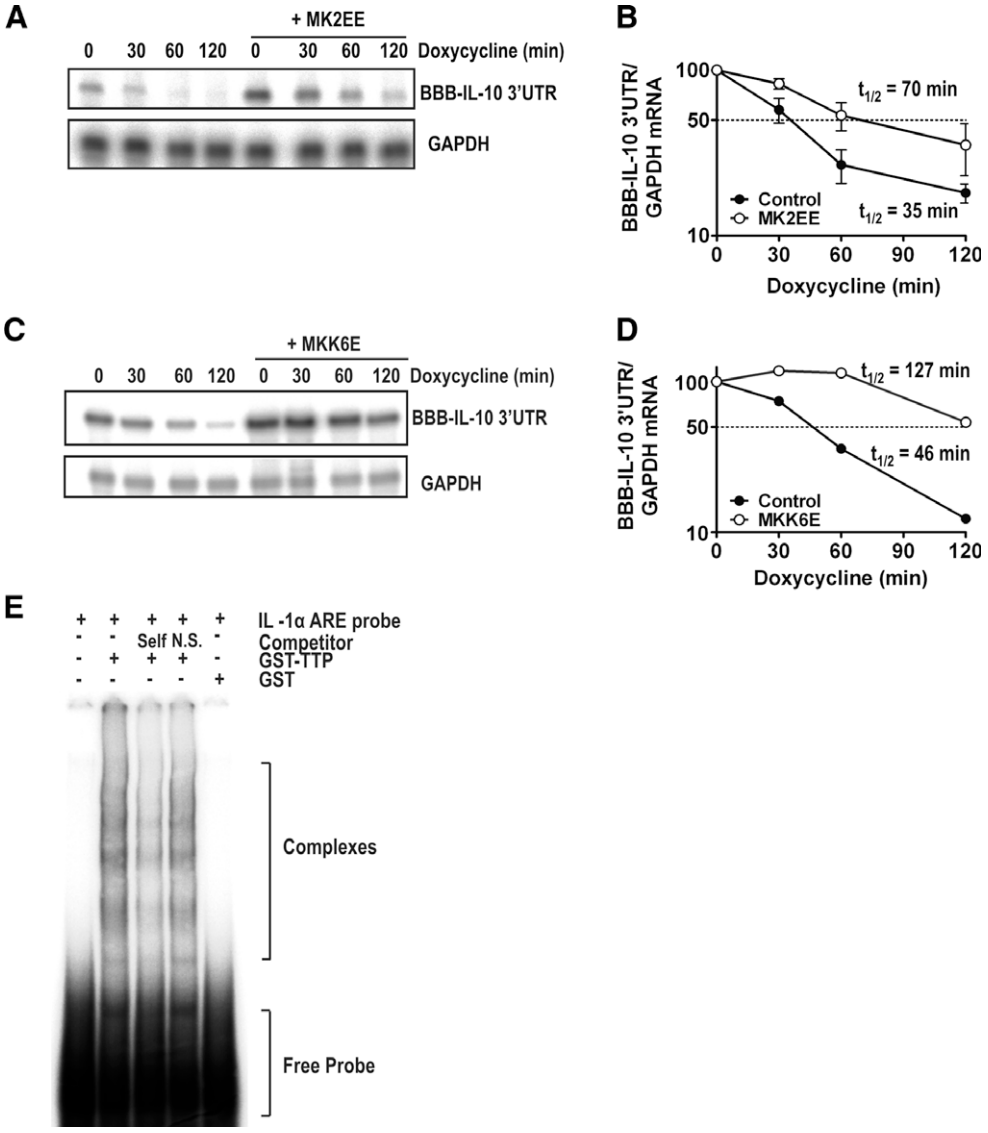

Fig. 2. Active mutants of MKK6 and MK2 stabilise an IL-10 3′UTR reporter mRNA and TTP binds specifically to the IL-1α ARE. HeLa tet-off cells were transfected with BBB-IL-10 3′UTR reporter and MKK6E or MK2EE expression plasmids. After 24 h doxycycline was added to block transcription and BBB-IL-10 3′UTR and GAPDH mRNAs were measured by RPA. (A and C) Phosphorimages of RPAs. Plots of mean normalised mRNA and S.E.M. for three experiments (B) or representative of 3 experiments with different timepoints (D). (E) ^{32}P end-labelled IL-1α ARE RNA probe (0.1 pmol) was incubated with GST–TTP (100 ng) or GST (100 ng) in the absence or presence of 1 pmol of unlabelled self or N.S. (non-self) competitor RNAs. RNA–protein complexes were resolved by electrophoresis and visualised using a phosphorimager. The bands representing the free probe and the TTP-RNA complexes are indicated. Four clear complexes are visible, consistent with multiple TTP binding sites in the IL-1α 3′UTR. The result is representative of three experiments.

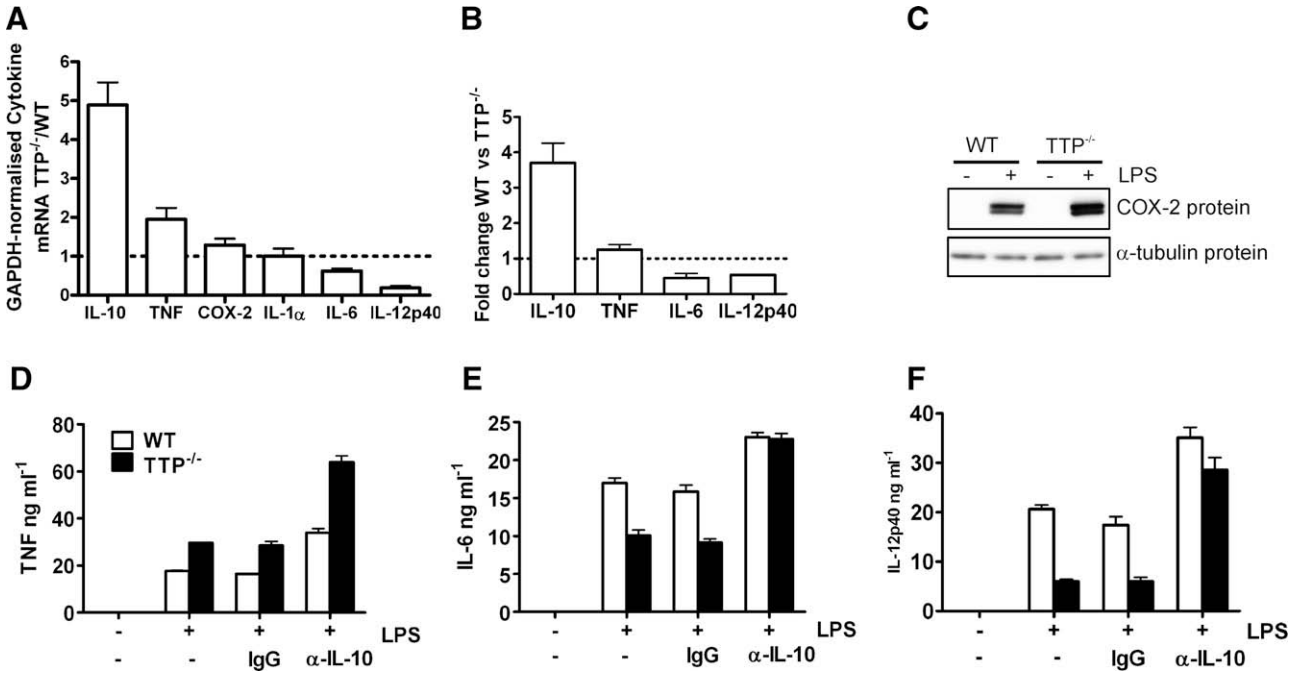

Fig. 3. Inflammatory response mRNA and protein expression in wild-type and $TTP^{-/-}$ BMDM in the absence or presence of IL-10 neutralisation: (A) Wild-type and $TTP^{-/-}$ BMDM were treated with LPS for 4 h and inflammatory response mRNAs (A) were measured as in Fig. 1, and proteins (B and C) by ELISA and Western blotting, respectively. (A) Graph shows mean fold-induction of inflammatory response mRNAs normalised to GAPDH in $TTP^{-/-}$ relative to wild-type BMDM for 3 independent experiments. Dotted line indicates that expression is the same in wild-type and $TTP^{-/-}$ cells. (B) Graph of inflammatory response proteins for (A). (D–F) Cells were either left untreated, or pre-treated with an anti-IL-10 antibody for 1 h and then incubated for a further 16 h in the presence of LPS. TNF (D), IL-6 (E) and IL-12p40 (F) in culture medium was measured by ELISA.

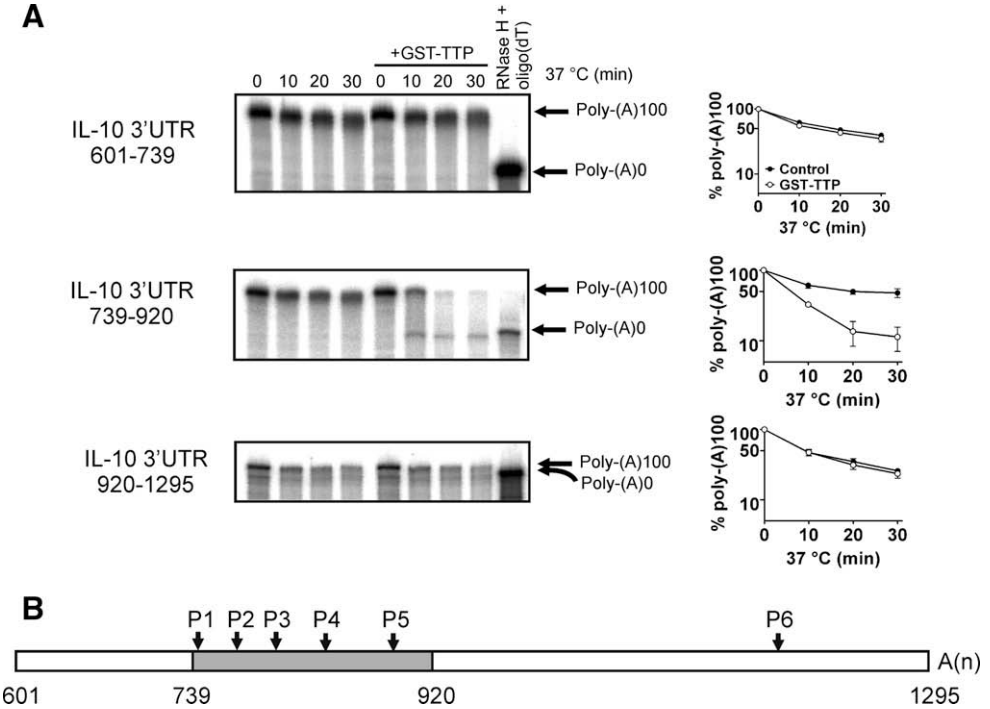

Fig. 4. TTP directs deadenylation of an IL-10 RNA in vitro. (A) Radiolabelled poly-(A) RNA substrates were produced by in vitro transcription and incubated with 5 μg HeLa S100 in the presence or absence of 100 ng of GST–TTP for the times shown. Representative phosphorimages and graphs of mean and S.E.M. for three experiments are shown. In the final lanes RNA substrates were deadenylated by treatment with oligo(dT) and RNaseH. The positions of poly-(A)100 and poly-(A)0 bands are indicated. (B) Schematic of IL-10 3′UTR showing AUUUA pentamers (P1–6).

3′UTR. Addition of GST–TTP resulted in rapid decay of IL-10 3′UTR 739–920 RNA but had no effect on the decay of the other two substrates (Fig. 4). The decay of IL-10 3′UTR 739-920 in the presence of TTP was accompanied by the appearance of a higher mobility intermediate. It migrated to a similar position to a poly(A)-lacking transcript, consistent with it being a deadenylated intermediate. Hence, TTP recognises the central (ARE-containing) portion of IL-10 mRNA to target it for deadenylation.

4. Discussion

We show that p38 MAPK-mediated inhibition of TTP-directed decay represents a more general mechanism for mRNAs of the inflammatory response in BMDM than previously suggested. We confirm that TTP plays an important role in regulating IL-10 since steady-state IL-10 mRNA and IL-10 protein were found to be upregulated in LPS-treated $TTP^{-/-}$ BMDM and an IL-10 RNA was directly regulated by TTP in vitro. p38 MAPK not only regulates cytokine expression at the post-transcriptional level but also upregulates transcription. Regulation of IL-10 transcription by p38 MAPK has been shown to involve Sp1 [16] and the downstream kinases MSK1 and MSK2 that phosphorylate CREB [17]. These kinases also regulate TTP mRNA production [18].

Since many of the mRNAs examined were relatively stable in the absence of inhibitor in both wild-type and $TTP^{-/-}$ cells, the employment of p38 MAPK inhibitor in Act D chases revealed targets of TTP which would otherwise not have been identified. This could explain why of the mRNAs found to be regulated by TTP and p38 MAPK in this study, only IL-10 and TNF have previously been identified as TTP targets.

In a recent report describing p38α MAPK-depleted macrophages, no effect on inflammatory mediator mRNA stability was observed [19]. This is probably because p38 MAPK activity is needed for both, the induction of TTP by LPS [11] and subsequent mRNA decay, since pre-treatment of macrophages with p38 MAPK inhibitor prior to stimulation with LPS fails to destabilise TNF mRNA. Given the recent failure of p38 MAPK inhibitors in clinical trials, TTP and MK2 now represent important downstream targets for therapies aimed at treating chronic inflammatory diseases such as rheumatoid arthritis. Ideally, such therapies would specifically block the expression of pro-inflammatory mediators, such as TNF, whilst sparing anti-inflammatory IL-10. Since the same post-transcriptional mechanism regulates pro-inflammatory mediator mRNAs and anti-inflammatory IL-10 mRNA, the utility of MK2- and TTP-targeted therapies aimed at treating chronic inflammatory diseases may depend on the specific contribution of these cytokines to the disease.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.febslet.2009.04.039.

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