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Post-transcriptional gene regulation by MAP kinases via AU-rich elements

Andrew Clark, Jonathan Dean, Corina Tudor, Jeremy Saklatvala

Kennedy Institute of Rheumatology Division, Imperial College London, 1 Aspenlea Road, Hammersmith, London W6 8LH, UK

TABLE OF CONTENTS

1. ABSTRACT

Eukaryotic cells must continuously sense their environments, for example their attachment to extracellular matrix and proximity to other cells, differences in temperature or redox conditions, the presence of nutrients, growth factors, hormones, cytokines or pathogens. The information must then be integrated and an appropriate response initiated by modulating the cellular programme of gene expression. The mitogen-activated protein kinase (MAPK) signaling pathways play a critical role in this process. Decades of research have illuminated the many ways in which MAPKs regulate the synthesis of mRNA (transcription) via phosphorylation of transcription factors, cofactors, and other proteins. In recent years it has become increasingly clear that the control of mRNA destruction is equally important for cellular responses to extracellular cues, and is equally subject to regulation by MAPKs. This review will summarize our current understanding of post-transcriptional regulation of gene expression by the MAPKs and the proteins that are involved in this process.

2. INTRODUCTION

The orderly and regulated flow of genetic information from DNA to protein, from genome to proteome, requires that the intermediate molecule, mRNA, is relatively short-lived. Where gene expression undergoes dynamic changes, rapid turnover of mRNA is typically observed. For example mRNAs involved in cell cycle progression, immune and inflammatory responses often have short half-lives. In contrast housekeeping genes that are expressed at a relatively constant level typically produce more stable mRNAs (1). In other words mRNA degradation is controlled in a transcript-specific manner. In most cases the rate of degradation of an mRNA is controlled by sequences within its untranslated regions (UTRs). These regions are unconstrained by the selective pressures that direct the evolution of protein coding sequences, and have acquired complex roles in the regulation of mRNA translation and localisation as well as turnover.

Post-transcriptional regulation of gene expression is comprehensively reviewed elsewhere (2, 3), and only a

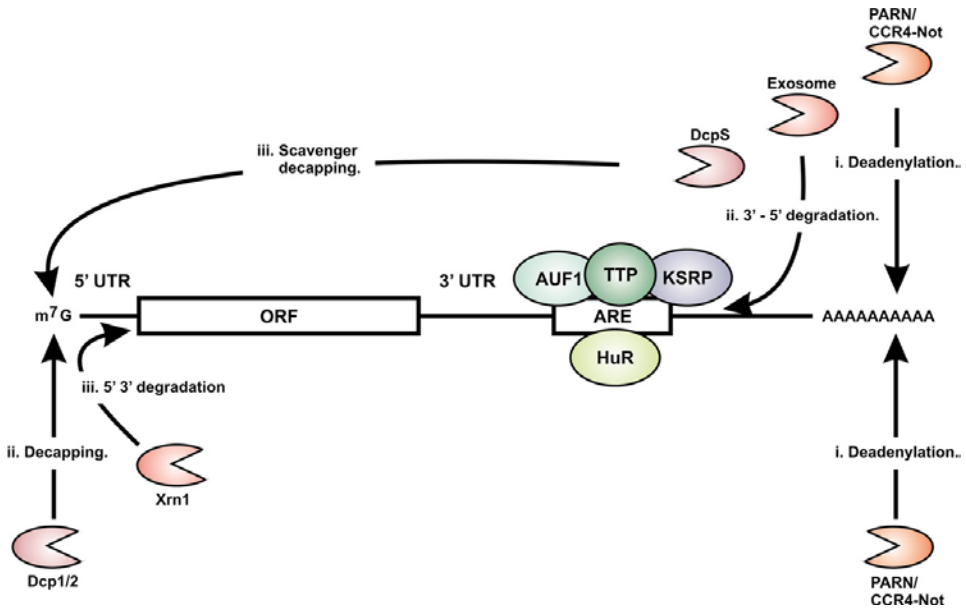

Figure 1. Pathways of mRNA degradation. The open reading frame (ORF) is flanked by 5' and 3' UTRs. An ARE in the 3' UTR provides binding sites for proteins such as HuR, AUF1, TTP and KSRP (see text). The 3' to 5' decay pathway (shown above the mRNA) involves sequential action of the deadenylase PARN or the Ccr4/Not complex, degradation of the mRNA body by the exosome, and 5' end processing by the scavenger decapping complex (DcpS). The 5' to 3' decay pathway (shown below the mRNA) has the same initial deadenylation step, then a decapping complex (including the decapping proteins Dcp1 and 2) removes the 7 methyl guanosine, and the mRNA body is degraded by the nuclease Xrn1. For simplicity not all components of the mRNA degradation machinery are illustrated.

very brief overview will be given here (Figure 1). In general the rate limiting step in mRNA degradation is the shortening of the poly- (A) tail with which the 3' end is decorated. This can be catalysed by a number of different deadenylases or deadenylase complexes. Once the poly (A) tail has been shortened beyond a critical length, the body of the mRNA becomes susceptible to rapid destruction by one of two pathways. The first pathway involves the exosome, a large complex of exonucleases and helicases responsible for processive degradation from the 3' end. When the bulk of the mRNA has been destroyed and only a short oligoribonucleotide remains, a scavenger decapping complex removes the 7-methyl-guanosine cap from the 5' end. Alternatively, the mRNA can be degraded by the exonuclease Xrn1, which degrades in the 5' to 3' direction. This pathway requires the initial removal of the 7-methyl-guanosine cap, which is catalysed by a decapping complex distinct from the scavenger decapping complex mentioned above. Both pathways for mRNA degradation are extremely rapid, and intermediates are difficult to detect. It was initially believed that the 3' to 5' exosome-dependent pathway predominated in mammalian cells, but more recent evidence suggests that the 5' to 3' pathway may be equally important (2, 4). RNA degradation may occur at discrete cytoplasmic granules known as processing bodies or P-bodies, which are also implicated in micro-RNA mediated post-transcriptional silencing and RNA surveillance pathways (5-7).

Regulatory elements in UTRs are recognized in a sequence-specific manner by RNA-binding proteins. Whilst other classes of regulatory element and their binding proteins are increasingly recognized, the best characterized regulatory sequences at present are the adenine/uridine-rich elements (AREs), first described as mRNA destabilizing elements in 1986 (8, 9). In a commonly used classification based on the presence of pentameric AUUUA motifs, type I AREs contain dispersed pentamers, type II AREs contain overlapping pentamers, and type III AREs contain no pentamers but are generally U-rich . Other classification systems have also been proposed (10). The nonameric sequence UUAUUUAUU was identified as a minimal destabilizing sequence (11, 12), but other ARE sequences may function equally well, depending on the context in which they are found.

Many ARE binding proteins have been identified, and shown to recognize AREs with overlapping but subtly different sequence specificities (2, 3). Amongst these proteins, tristetraprolin (TTP) and two closely related proteins are well-characterized mRNA destabilizing factors, as is the KH-domain splicing regulatory protein (KSRP). Human antigen R (HuR), a widely-expressed member of the ELAV (embryonic lethal abnormal vision) family of RNA binding proteins, is a stabilizing factor. ARE/poly (U)-binding degradation factor 1 (AUF1) may either promote or inhibit mRNA degradation, depending on the cellular context and which of the four alternatively spliced isoforms are expressed. Destabilizing factors recruit components of the RNA degradation machinery to specific mRNAs, or cause those RNAs to become localized at sites of degradation, or nucleate the formation of processing bodies (13-20). In effect these may amount to the same thing.

Table 1. Targets of post-transcriptional regulation by the three major MAPK pathways

p38 MAPK	ERK	JNK
	β-APP (254)	
	β-AR (255)	
BMP-2 (211)		
Catalase (212)		
CCL2 (29, 89, 90, 213, 214)	CCL2 (90, 214)	
CCL3 (29, 215)		
C/EBPδ (172)		
COX-2 (75, 171, 175, 216-225)	COX-2 (223, 256, 257)	
CSF2 (72, 78, 226-228)	CSF2 (200)	
CXCL1 (78, 146, 229, 230)		
CXCL2 (78)		
CXCL3 (29)		
CXCL8 (72, 87, 187, 228, 231-236)		
CXCL10 (29, 237-239)		
DUSP1 (240)		
γ-GCSH (174)		
Ier3 (162)		
IFN-γ (73, 241)		
IL-1β (29, 230)		
IL-2 (241)		IL-2 (98, 99)
IL-3 (242)		IL-3 (262)
IL-4 (243)		
IL-6 (215, 227, 244-247)		
IL-13 (243)		
		iNOS (263, 264)
myogenin (186)		
	nucleolin (258)	
p21 (186)	p21 (259, 260)	
PAI-1 (248)		
Socs3 (249)		
Sox9 (250)		
	TGFβ (261)	
TNF (50, 52-55, 60, 77, 84, 85, 215, 239, 251)	TNF (52, 91-93)	
UPA (76, 252)		
VEGF (253)	VEGF (163)	VEGF (253)

This is not an exhaustive list

mRNA fate is thought to be determined by the combinatorial actions of multiple proteins that recognize overlapping or discrete sequences within UTRs. In ways that are not yet fully understood, their binding is likely to be influenced by the secondary structure of the mRNA, which in turn may be influenced by ionic conditions (21) or intermolecular RNA-RNA interactions (22). The cellular machinery dedicated to the destruction of RNA is therefore highly complex, with many possible points of regulation. Indeed, the process of mRNA turnover is under tight regulation, and can be modulated in response to extracellular cues. Hence changes in mRNA abundance can be brought about by changes in rate of synthesis, destruction or both. Post-transcriptional mechanisms can function cooperatively with transcriptional mechanisms to accelerate or amplify changes in steady state mRNA levels. Alternatively, transcriptional and post-transcriptional mechanisms can oppose one another to dampen changes in steady state mRNA levels.

Researchers have recently used microarray-based approaches to assess the relative contributions of transcriptional and post-transcriptional regulatory events during a coordinated cellular response (23, 24). For example changes in steady state cytoplasmic mRNA abundance were compared to changes in newly synthesized nuclear pre-mRNA, the latter providing a crude measure of the transcriptional response (25, 26). It was concluded that approximately half of the global change in mRNA levels could be accounted for by transcriptional regulation. By inference, the remainder must be explained by changes in mRNA stability. More directly, other researchers have combined microarrays with actinomycin D chases to study mRNA stability at a transcriptome-wide level (27-30). Half-lives of many thousands of mRNAs were increased or decreased in the course of a cellular response to a simple agonist. Such studies underline the point that changes in cellular programmes of gene expression cannot be understood in terms of transcription alone. It is increasingly recognized that alterations in post-transcriptional regulatory mechanisms can have a causative role in human pathologies, for example cancers and chronic inflammatory diseases (31-35). Conversely, the post-transcriptional level of gene regulation represents a possible new target for therapeutic intervention in human disease (36, 37).

The principles of transcriptional regulation by signaling pathways are quite well understood. In contrast the study of mRNA turnover regulation is in its infancy. This review will focus on modulation of mRNA stability by MAPKs, highlighting gaps in our current understanding of this phenomenon. Table 1 lists mRNAs that have been identified as targets of post-transcriptional regulation by the three major MAPK pathways. There is more abundant evidence for post-transcriptional regulation by p38 than by ERK or JNK, therefore our review will begin with the p38 MAPK pathway.

3. POST-TRANSCRIPTIONAL REGULATION BY MAPK PATHWAYS

3.1. p38 MAPK

The four members of the p38 MAPK family, αβγ and δ, are encoded by discrete genes and display different patterns of tissue-specific expression (38). The α isoform is very broadly expressed whereas the other isoforms are expressed in a more restricted fashion. The first member of the family, p38α, was identified at about the same time by three labs as a component of a signaling pathway activated by the pro-inflammatory cytokine interleukin 1 (IL-1) or by stresses such as heat shock or hyperosmolarity, and as the molecular target of a novel compound that post-transcriptionally inhibited the expression of IL-1 and another potent inflammatory cytokine, tumor necrosis factor (TNF). Since its discovery, the p38 MAPK pathway has therefore been intimately linked to both inflammation and post-transcriptional regulation. In the canonical pathway an upstream MAPK kinase (usually MKK3 or MKK6) activates p38 MAPK by phosphorylating both threonine and tyrosine residues within the Thr-Gly-Tyr activation motif. Alternative pathways for p38 MAPK activation exist, one involving phosphorylation of a tyrosine residue near the carboxy terminus (39). It is conceivable that this phosphorylation modulates the interaction of p38 MAPK with downstream substrates, and that therefore the outcome of p38 MAPK activation depends upon the pathway by which it becomes active. It

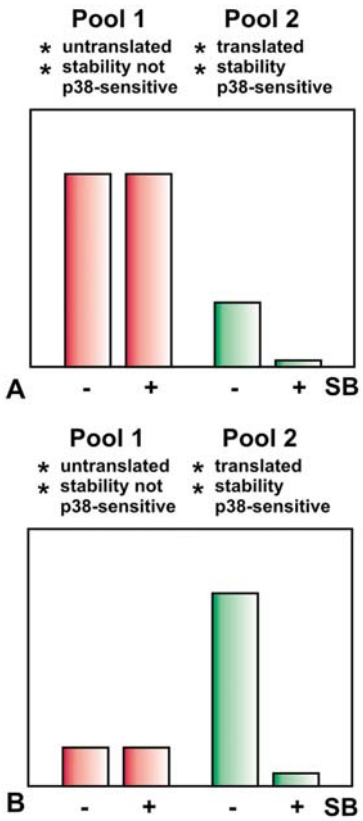

Figure 2. A hypothetical reconciliation of p38 MAPK effects on stability and translation of TNF mRNA. Suppose that there are two cellular pools of TNF mRNA: pool 1 is unavailable for translation but not subject to p38-regulated degradation, whilst pool 2 is translatable but rapidly degraded in the absence of p38 activity. Imagine that in one cell type or under one set of conditions (**A**) most TNF mRNA is in pool 1. Addition of a p38 inhibitor will result in rapid clearance of the mRNA in pool 2 and consequent inhibition of TNF protein synthesis, but little change in stability or steady state quantities of TNF mRNA at the whole cell level. Inspection of polysomal profiles will reveal that the inhibitor has decreased the amount of polysome-associated TNF mRNA. One possible conclusion is that p38 MAPK controls TNF mRNA translation. Now, suppose that in another cell type or under different conditions (**B**) most TNF mRNA is in pool 2. Addition of a p38 inhibitor will decrease the expression of TNF mRNA and protein to quite similar extents, and destabilization of TNF mRNA will be readily demonstrated by actinomycin D chase experiments. The conclusion is that p38 MAPK controls TNF mRNA stability. The two scenarios differ only in the distribution of TNF mRNA between subcellular pools. In the first scenario it is true to say that TNF mRNA is translationally repressed, but it is not translationally regulated by p38 MAPK.

has not yet been investigated whether non-canonical p38 MAPK activation has different consequences in terms of post-transcriptional gene regulation.

SK&F 86002, the original p38 inhibitor, has given rise to second and third generation inhibitors such as SB203580 and SB202190, with improved specificity and efficacy. These drugs, which have played an essential part in the elucidation of the post-transcriptional function of the p38 MAPK pathway, do not inhibit the γ or δ isoforms (40). A recently described class of MAPK inhibitors is mechanistically dinstinct from the original family of dipyridinyl imidazoles, and blocks the function of all four isoforms (41). Such compounds may be used to determine whether p38 γ and δ are involved in the post-transcriptional regulation of gene expression. They clearly differ in substrate specificity from the α and β isoforms (38), and there is yet little or no evidence for a post-transcriptional role. Henceforth "p38" will be assumed to refer to the α and β isoforms.

Because of the central role of the p38 MAPK pathway in the regulation of inflammatory gene expression, it is regarded as a promising target for therapeutic intervention in chronic inflammatory diseases such as rheumatoid arthritis or Crohn's disease (42, 43). Several p38 MAPK inhibitors have undergone or are undergoing clinical trials (44). It needs to be kept in mind that the function of p38 MAPK is not restricted to the control of inflammatory gene expression. For example muscle differentiation requires the p38-dependent expression of transcription factors such as MyoD and myogenin (45, 46). Other roles in cell proliferation and survival, differentiation or development have been described (38). It is not yet apparent whether these additional p38 functions will give rise to significant problems in the clinical development of p38 inhibitors as anti-inflammatory drugs (47).

Early papers concluded that the p38 MAPK pathway was required for the efficient translation of TNF mRNA, because inhibitors reduced TNF expression more strongly at the protein level than at the mRNA level (48, 49). However, recent research (Table 1) has revealed that control of mRNA stability is a more frequently encountered property of the p38 pathway. In fact, several studies describe destabilization of TNF mRNA by p38 inhibitors (50-55). As described below, mechanisms of regulation of mRNA turnover by p38 MAPK are increasingly well understood, but an account of transcript-specific translational control by this pathway is still lacking.

It is technically difficult to quantify changes in translation efficiency in isolation from mRNA degradation. In the absence of such direct assays, translational control is often inferred from inspection of polysomal profiles or from discrepancies between mRNA and protein levels. In the case of TNF the correlation between mRNA and protein expression tends to be poor (56-60). Even under strongly inducing conditions, a relatively low proportion of TNF mRNA may be actively translated and associated with polysomes (48, 60-63). Deductions from mRNA and protein abundance can be misleading if discrete subcellular pools of TNF mRNA are not identically regulated by signaling pathways. For example (Figure 2) suppose that there exists a subcellular pool of TNF mRNA (pool 1), which is unavailable for translation and not regulated by p38 MAPK at the level of mRNA stability. In contrast, p38 MAPK controls the stability of a second, discrete

subcellular pool (pool 2), which is available for translation. If the majority of TNF mRNA is in pool 1, then inhibition of p38 will strongly decrease expression of TNF protein but not strongly decrease whole-cell levels of TNF mRNA. Inhibitors of p38 MAPK are reported to decrease the proportion of TNF mRNA associated with polysomes (48, 62), which has been interpreted as suggesting that p38 promotes the translation of TNF mRNA. However there is not yet direct evidence that TNF mRNA can be mobilized between untranslatable and translatable pools in a manner that is controlled by p38 MAPK. An alternative interpretation of the same data is that inhibition of p38 MAPK causes the degradation rather than the translational suppression of polysome-associated TNF mRNA.

Effects of p38 MAPK on mRNA translation certainly cannot be ruled out, although the lack of a mechanistic explanation is problematic, and the supporting evidence is not as conclusive as it may appear. The RNA binding proteins TIA-1, TIAR and FXR1P have been implicated in the sequestration and translational blockade of TNF mRNA (62, 64, 65). It is possible that one or more of these proteins acts downstream of the p38 MAPK pathway to control translation of TNF and other mRNAs, but such a role has not yet been demonstrated. Transcriptional pulsing strategies can be used to generate synchronized pools of reporter mRNAs with similar poly (A) tail lengths (66). This method was used to show that p38 activation inhibits the deadenylation of a reporter mRNA containing the TNF ARE, without influencing the rate of subsequent decay of the mRNA body (67). Poly (A) tail length influences the efficiency of mRNA translation as well as its stability. In theory, control of deadenylation by p38 MAPK could provide a mechanistic link between effects of the pathway on mRNA translation and stability. However, it is not yet well established that p38 MAPK controls stability of endogenous ARE-containing transcripts at the level of deadenylation.

The downstream kinase MAPK-activated protein kinase 2 (MAPKAP-K2 or MK2) is efficiently phosphorylated and activated by p38 α and β but not by the γ and δ isoforms (38, 68-71). Several lines of evidence suggest that MK2 has an important role as an effector of post-transcriptional regulation by the p38 MAPK pathway. Constitutively active mutants of MK2 were able to stabilize a variety of ARE-containing reporter transcripts (72-76). An MK2 null mouse was viable but underexpressed several inflammatory mediators that are post-transcriptionally regulated by the p38 MAPK pathway (71, 77-79), and was consequently resistant to various inflammatory challenges (80-83). Initially, steady state levels and stability of TNF mRNA were found to be unaltered in $MK2^{-/-}$ cells in spite of an approximately 90% decrease in expression of TNF protein, consistent with regulation of TNF translation by the p38 MAPK pathway (77). However, on further investigation, both TNF and IL-6 mRNAs were found to be less stable in cells lacking MK2 (79, 84). In embryonic fibroblasts derived from $MK2^{-/-}$ mice, a subset of mRNAs (including, CSF2, CXCL1, CXCL2, COX-2) were unstable in the presence of LPS but could be stabilized by reintroduction of MK2 (78), implying that LPS-induced stabilization requires the activation of MK2.

The kinase MK3 is highly related to MK2 and appears to overlap in function. The dominant role of MK2 in post-transcriptional regulation may simply reflect its higher level of expression in the cell types that have been studied. A murine knockout of MK3 alone had no obvious consequences, but in an MK2 null background caused a further decrease in the expression of TNF. Furthermore MK3 was indistinguishable from MK2 in its ability to rescue mRNA stabilization in $MK2^{-/-}$ MEFs (78). The functions of MK2 and MK3 have been investigated mainly in the context of inflammatory gene expression. An unanswered question is to what extent the regulation of mRNA stability is independent of MK2 or MK3, in other words directly mediated by p38 MAPK itself. It would be interesting to determine which mRNAs, if any, are destabilized by p38 inhibitors in the absence of both MK2 and MK3. Since different mechanisms of post-transcriptional regulation by the p38 pathway might predominate in different cell types, it would be instructive to carry out such an analysis in, for example, muscle cells as well as fibroblasts or macrophages.

The TNF ARE is essential for post-transcriptional control of TNF expression by p38 MAPK, since germline deletion of this element rendered TNF biosynthesis insensitive to p38 inhibitors (85). AUUUA motifs are common to p38-regulated transcripts (86), but their number and organization is extremely variable. A relatively complex arrangement of AUUUA motifs appeared to be necessary for regulation of COX-2 or IL-8 mRNA stability by the p38 pathway (87, 88). Amongst p38-stabilized mRNAs identified in a microarray study (29) common features of ARE sequence or structure could not be identified. Just as importantly, many unstable ARE-containing transcripts were not sensitive to p38 inhibition. Therefore, one of the greatest remaining puzzles in this field is how selective regulation of mRNA stability by the p38 pathway is achieved. To understand this fully it may be necessary to consider the secondary structure of RNA in which protein binding sites are embedded, or higher order features of ARE organization that have not yet been recognized.

3.2. ERK and JNK

Stability of several mRNAs has been shown to be regulated by the extracellular signal-regulated kinase (ERK) pathway (Table 1). There is considerable overlap with the set of transcripts regulated by p38 MAPK. Furthermore, CXCL2 and TNF mRNAs were cooperatively stabilized through the action of p38 MAPK and ERK (52, 89-91). The possible significance of convergence of the two signaling pathways is discussed below.

In macrophages the activation of ERK is required for the efficient export of TNF mRNA from the nucleus to the cytoplasm (92). The TNF ARE is necessary but not sufficient for this regulation, and ARE-binding proteins involved have so far not been identified (92, 93). The

regulation of TNF mRNA export is dependent on nuclear splicing of pre-mRNA and assembly of a complex of proteins at the splice site (93). Few other examples of ERK-regulated nuclear-cytoplasmic mRNA transport are known (94), and details of the mechanism await clarification.

The c-Jun N-terminal kinase (JNK) pathway was implicated in post-transcriptional regulation of IL-2 and -3, TNF, inducible nitric oxide synthase (iNOS) and vascular endothelial growth factor (VEGF) (references in Table 1). The synthetic glucocorticoid dexamethasone (dex) was reported to block TNF translation by inhibiting JNK activity in a mouse macrophage cell line (95). Dex also inhibits p38 MAPK in murine macrophages by inducing the expression of MAPK phosphatase 1 (57, 96, 97), therefore the inference that JNK controls translation may be mistaken. JNK-mediated stabilization of IL-2 mRNA was dependent on both an ARE in the 3' UTR and an element in the 5' UTR, designated the JNK response element (JRE) (98, 99). The JRE was recognized by nucleolin, an abundant nucleolar protein (100), and Y-box factor 1 (YB-1), a promiscuous nucleic acid binding protein (101). Depletion of these factors impaired JNK-mediated mRNA stabilization *in vitro*. However, neither protein appears to be a genuine substrate of JNK or a direct regulator of mRNA degradation. Their roles in mRNA turnover downstream of JNK may be rather indirect (99). Direct mechanistic links between JNK and mRNA stability or translation remain elusive.

3.3. MAPK signal integrating kinases

MAPK signal-integrating kinases (Mnks) can be activated by either p38 MAPK or ERK, and are therefore potential mediators of cooperative effects of the two MAPK pathways on gene expression (102, 103). Mnks are thought to influence higher order structure of mRNAs and control translation by phosphorylating the eukaryotic translation initiation factor eIF4E, which binds to the 5' cap structure (references in 104). It is unclear how this mechanism could result in selective post-transcriptional regulation of particular transcripts, since the 5' cap is a universal feature of eukaryotic mRNAs. Therefore it is of interest that Mnks are also able to phosphorylate $hnRNPA_0$, $hnRNPA_1$ and polypyrimidine tract binding protein-associated splicing factor (PSF) (104, 105). All of these proteins have been shown to interact with AREs, although precise specificities are not known. A Mnk inhibitor, CGP57380, decreased the expression of TNF in Jurkat T cells (104), murine macrophages (106) human keratinocytes (107) and the murine macrophage cell line RAW264.7 (108). The same inhibitor increased the association of TNF mRNA with $hnRNPA_1$ but decreased its association with PSF in Jurkat cells (104, 105). Mnks are proposed to regulate the translation (104, 106) and/or stability (108) of TNF mRNA through the phosphorylation of one or more associated RNA binding proteins. The specificity of CGP57380 is imperfect (40), therefore it would be extremely valuable to confirm these findings in the Mnk1/Mnk2 knockout mouse (109).

4. MEDIATORS OF POST-TRANSCRIPTIONAL REGULATION BY MAPKS

4.1. Tristetraprolin

Tristetraprolin (TTP) is a member of a small family of RNA-binding proteins that recognize AREs via a conserved, central tandem zinc finger domain (110) (Figure 3). Amongst several alternative names, TTP is also known as ZFP36 (zinc finger protein of 36 kD). In general, TTP protein is weakly expressed under basal conditions but upregulated in response to a variety of agonists. At least in murine macrophages, the expression of TTP is dependent on p38 MAPK (74, 111, 112). TTP may bind to AREs within its own 3' UTR and autoregulate its expression (74, 113), although this idea remains controversial (114). The function of endogenous TTP protein has been investigated in cells of the myeloid lineage, and more recently in T cells (115, 116), B cells (117) and fibroblasts (114). In transient transfection experiments we observed destabilization of reporter mRNAs by quantities of exogenous TTP that were below the limit of detection. IL-1 or PMA induced the expression of TTP in HeLa cells, although the abundance of the protein remained so low that it could be detected only with some difficulty (our unpublished observations). Great care needs to be taken before describing a given cell line as "TTP null" (88, 118).

The TTP relatives BRF (butyrate response factor) 1 and 2 are also known as ZFP36-like proteins 1 and 2 (ZFP36L1 and ZFP36L2). At the mRNA level, ZFP36, ZFP36L1 and ZFP36L2 are expressed widely but at different levels in normal human tissues (119). The three proteins appear to bind RNA with similar specificity, and function identically as effectors of ARE-dependent mRNA decay, suggesting that redundancy may exist between the members of the family (15, 17, 120, 121). Yet murine knockouts of TTP and ZFP36L1 differ strikingly. The ZFP36L1 knockout is embryonic lethal, at least partly due to dysregulation of VEGF expression in the developing embryo (122, 123). As discussed below, the TTP knockout is not embryonic lethal but has an inflammatory phenotype. An authentic ZFP36L2-null mouse has not yet been generated (124). The ZFP36 proteins may serve different functions by virtue of different patterns of expression, subtle differences in RNA binding specificity that have so far escaped detection, or different mechanisms of regulation.

A number of studies have independently concluded that TTP specifically recognizes the sequence UUAUUUAUU (125-127). This sequence was highly enriched amongst transcripts that associated with TTP protein *in vivo* (128). Wright and colleagues (129) have solved the structure of a nonameric UUAUUUAUU oligoribonucleotide in complex with the RNA-binding domain of the ZFP36L2. A conformational change is thought to take place on binding of ZFP36L2 to its RNA substrate. The zinc finger domain of TTP is very closely related to that of ZFP36L2 and is thought to interact with substrate in a similar fashion, with a structural change induced by nucleic acid binding (126, 130). Like several other RNA-binding proteins, TTP can shuttle between the

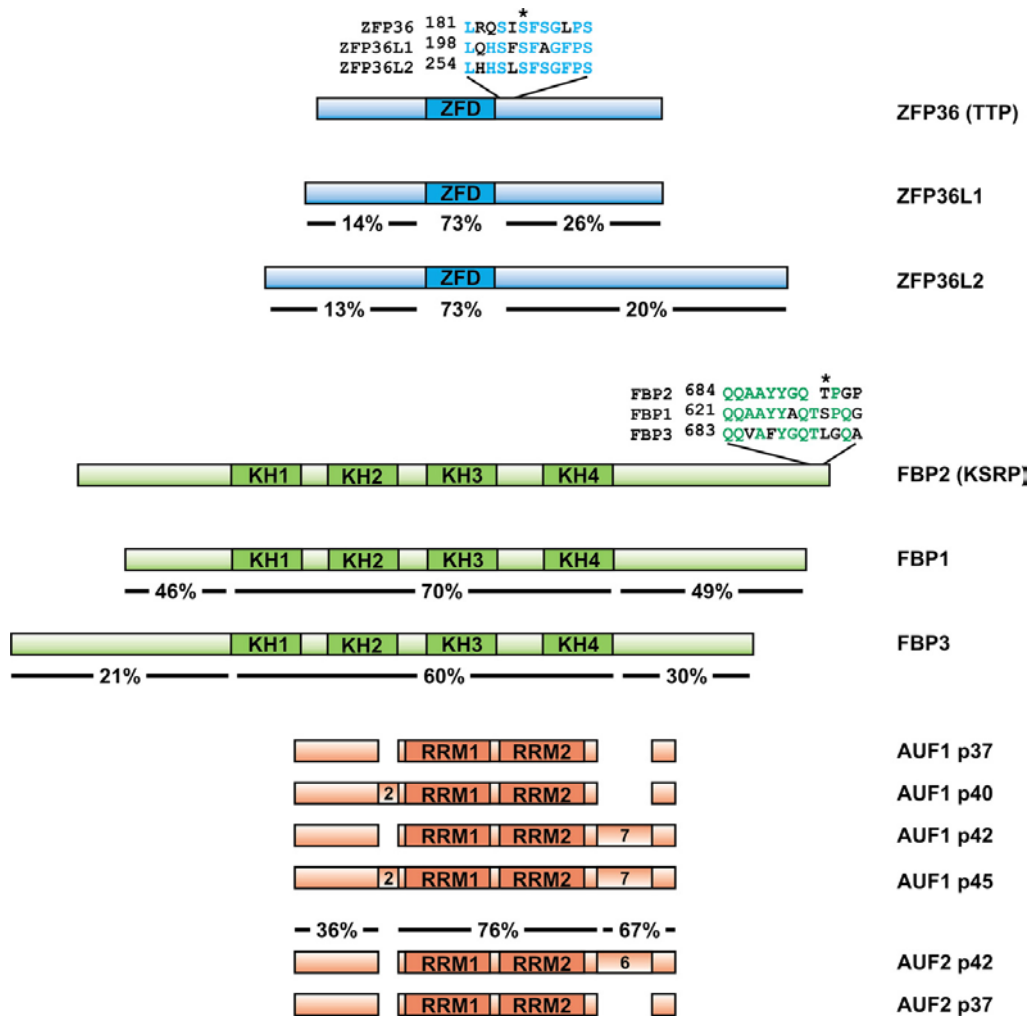

Figure 3. Properties of ARE-binding proteins. Members of the ZFP36/TTP family (blue), FBP/KSRP family (green) and AUF/hnRNP D family (red) are shown to scale. Zinc finger domains (ZFD), hnRNP K homology domains (KH) and RNA-recognition motifs (RRM) are indicated in solid colors. Percentages of identical residues within amino-terminal, central RNA-binding and carboxy terminal domains are indicated, in each case compared to the first protein in the alignment. Conservation of putative phosphorylation sites is illustrated, with amino acid sequences in the same order as the whole proteins. Residues conserved in two or more family members are in color, and sites of phosphorylation of TTP (S186) and KSRP (T692) are indicated by asterisks. In the case of the AUF family, alternatively spliced exons are indicated by numerals. The phosphorylation site S83 is encoded by exon 2, therefore is absent from AUF1 p37, AUF1 p42 and both splice isoforms of AUF2.

nucleus and the cytoplasm, but is almost exclusively cytoplasmic under most conditions. Several protein motifs have been implicated in the nuclear export and import of TTP (131-135). Of most direct relevance, the binding of 14-3-3 proteins to serine 178 was implicated in the cytoplasmic accumulation of murine TTP (135). 14-3-3 proteins are multifunctional adaptor proteins that specifically recognize serine- or threonine-phosphorylated partner proteins and control phosphorylation-dependent phenomena such as subcellular localization and protein stability (136-138). The implication is that cytoplasmic localization of TTP is partly dependent on phosphorylation of serine 178, as we will discuss below.

In vitro and in transfected cells TTP promotes the deadenylation of ARE-containing reporter transcripts (20, 139-141). Furthermore TTP and ZFP36L1 interact with several components of the cellular mRNA degradation machinery, including deadenylases, decapping complexes and exonucleases (14, 15, 17, 18, 20). Tethering of TTP protein to reporter mRNAs resulted in localization of those transcripts to processing bodies and rapid degradation (14, 15, 17). Depletion of TTP and ZFP36L1 impaired, whereas overexpression of TTP or ZFP36L1 enhanced, the localization of ARE-containing reporter transcripts to processing bodies (17). In these studies exogenous TTP and TTP fusion proteins were expressed without deliberate activation or inhibition of the signaling pathways that are thought to control expression and function of endogenous TTP. It would be interesting to determine whether activation of MAPK signaling pathways and phosphorylation of specific residues influenced the

localization or turnover of a reporter transcript to which TTP was tethered.

The murine TTP knockout results in a complex inflammatory syndrome characterized by myeloid hyperplasia, cachexia, erosive arthritis, dermatitis and conjunctivitis (110, 142). Much of this pathology is due to enhanced stability of TNF mRNA and increased expression of TNF protein by cells of the myeloid lineage (142-144). The phenotype is likely to be influenced by dysregulation of other transcripts in both myeloid and other cell types. $TTP^{-/-}$ animals or cells show abnormal expression of CSF2 (colony stimulating factor 2, also known as granulocyte/macrophage colony stimulating factor), COX-2, IL-2, CXCL1 and a number of other immune/inflammatory mediators (116, 140, 145, 146) (our unpublished observations). Of particular interest, TTP directly controls expression of the potent anti-inflammatory cytokine IL-10 via its interaction with the IL-10 3' UTR (128) (our unpublished observations). Hence the TTP null phenotype may be a complex outcome of changes in expression of both pro- and anti-inflammatory mediators. In summary, TTP is well characterized as an important effector of ARE-dependent mRNA degradation. Several targets of TTP-mediated post-transcriptional regulation have been identified, and other putative targets are coming to light, for example through the systematic analysis of mRNA stabilities in TTP null fibroblasts (114) or by analysis of transcripts associated with TTP *in vivo* (128).

TTP is very extensively phosphorylated *in vivo* (112, 147-149). Mass spectrometric analysis identified ten major sites of phosphorylation of exogenously expressed TTP in HEK293 cells, as well as several minor sites (149). It should be noted that signaling pathways involved in the phosphorylation of TTP may not have been fully active in these cells, since no stimulus was applied. *In vitro* TTP could be phosphorylated by all three major MAPKs (147, 150-154), although sites of phosphorylation and functional consequences are not yet known. Since p38 MAPK regulates mRNA stability via MK2, it is significant that TTP is efficiently phosphorylated by MK2 *in vitro* (112). Two major sites of phosphorylation by MK2 were identified as serines 52 and 178 (of murine TTP) (155). There is evidence that both sites are phosphorylated *in vivo*, and that MK2 is at least partly responsible (149, 155, 156). Note that the sequence surrounding the distal phosphorylation site is quite well conserved in ZFP36L1 and ZFP36L2 (Figure 3). The corresponding site in ZFP36L1 has been implicated in the regulation of ZFP36L1 function by PKB (157).

$TTP^{-/-}$ macrophages were relatively insensitive to the inhibitory effect of p38 inhibitors on TNF gene expression, suggesting that post-transcriptional gene regulation by the p38 MAPK pathway may be mediated by TTP (150). Whereas $MK2^{-/-}$ mice underexpressed and $TTP^{-/-}$ mice overexpressed TNF, double knockout mice expressed roughly the same quantity of TNF as the TTP knockouts. Therefore MK2 regulates TNF biosynthesis chiefly by inactivating TTP (84). CXCL-1 mRNA was destabilized by a p38 inhibitor in wild type macrophages but not in $TTP^{-/-}$ macrophages (146). The same is broadly true of TNF, IL-10 and a number of other mRNAs (our unpublished observations). One exception is that TNF mRNA was very weakly (but statistically significantly) destabilized by p38 inhibition in $TTP^{-/-}$ macrophages. These observations demonstrate that the p38-MK2 pathway regulates the stability of certain inflammatory mediator mRNAs exclusively (or almost exclusively) via TTP (at least in murine macrophages).

It is clearly crucial to understand what MK2-mediated phosphorylation does to TTP. The phosphorylation of serines 52 and 178 increases the interaction of TTP with 14-3-3 proteins (155, 156, 158, 159), with a highly complex set of consequences (Figure 4). **1) Prevention of dephosphorylation.** The phosphorylation status of TTP is dynamically regulated by a balance of kinase and phosphatase activities (111, 156). The binding of 14-3-3 proteins protects TTP from PP2a-mediated dephosphorylation (156). The cellular equilibrium between phosphorylated and unphosphorylated TTP may therefore be set by 14-3-3 protein availability, although this remains to be tested. **2) Prevention of proteasome-mediated degradation.** In transfected cells, coexpression of 14-3-3 proteins increased the levels of TTP protein (135). MK2-dependent phosphorylation of serines 52 and 178 prevented the proteasome-mediated degradation of TTP protein, presumably because the recruitment of 14-3-3 proteins blocks targeting of TTP to the proteasome (84, 111). **3) Regulation of subcellular localization.** TTP can be detected in both stress granules (distinct cytoplasmic foci at which translationally silenced mRNAs are stored under conditions of cellular stress) and processing bodies (4, 6, 160, 161). Phosphorylation at serines 52 and 178 resulted in exclusion of TTP from stress granules (158). The significance of this is uncertain, because stress granules are not thought to be sites of mRNA degradation, and it is not known whether they are formed during a normal physiological response to a pro-inflammatory stimulus. In HeLa cells IL-1 caused transient relocalization of a GFP-TTP fusion protein from the nucleus to the cytoplasm in a manner dependent on p38 MAPK activation and intact serines 52 and 178 (our unpublished observations). The stabilization of TTP mRNA and protein by p38 MAPK (74, 84, 111) makes it difficult to observe endogenous TTP protein under conditions of chronic p38 inhibition. However, addition of a p38 inhibitor to macrophages that had previously been stimulated with LPS resulted in relocalization of pre-existing endogenous TTP to the nucleus (111). This is consistent with the previous observation that 14-3-3 proteins enhanced the cytoplasmic accumulation of TTP in a manner dependent on serine 178 (135), but its physiological significance is so far unknown. **4) Regulation of RNA binding activity.** MK2-mediated phosphorylation of serines 52 and 178 was suggested to decrease the affinity of TTP for cognate RNA (84), although other studies disagreed with this conclusion (155, 156, 158). **5) Regulation of mRNA-destabilizing activity.** Phosphorylation of serines 52 and 178 impaired the RNA destabilizing function of TTP. Wild type TTP destabilized an ARE-containing reporter but was inactivated by MK2, whereas a serine 52/178 mutant destabilized the reporter and was unresponsive to MK2 (158).

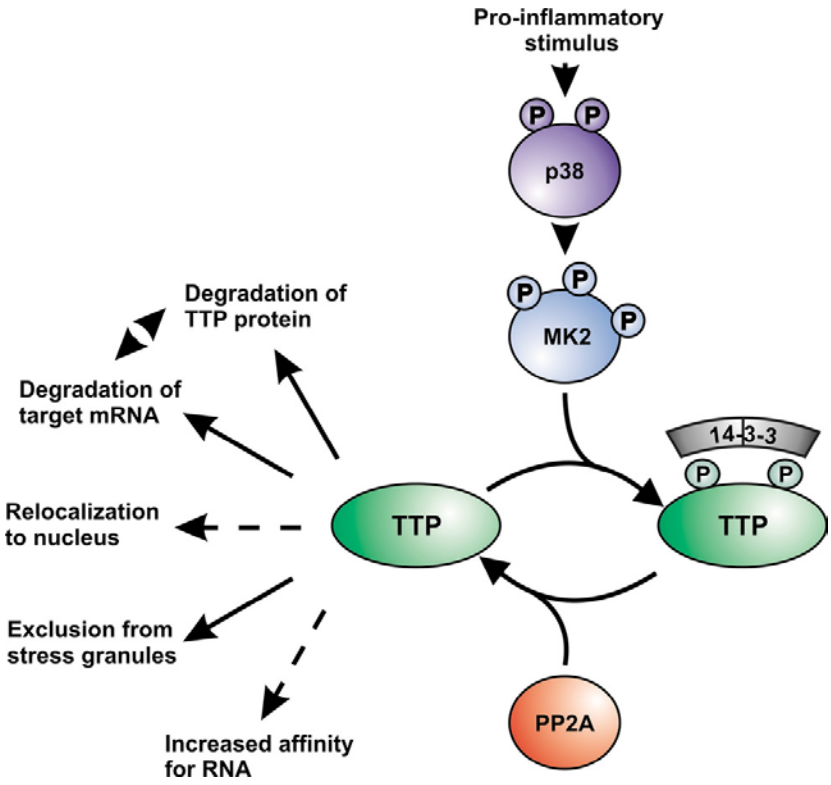

Figure 4. Regulation of TTP by the p38-MK2 pathway. In this simplified schematic, only MK2 mediated phosphorylations of TTP are considered. An equilibrium exists between phosphorylated and unphosphorylated TTP. The position of the equilibrium is influenced by 14-3-3 proteins, which bind to phosphorylated TTP and protect it from dephosphorylation by PP2A. Dephosphorylated TTP protein is excluded from stress granules and prone to degradation by the proteasome, but more active in the degradation of target transcripts. The role of MK2-mediated phosphorylation in the nuclear-cytoplasmic distribution of TTP is not well established; the effect of MK2-mediated phosphorylation on the affinity of TTP for RNA is controversial; and the link between degradation of TTP protein and TTP-bound mRNAs is uncertain (dotted arrows).

The p38 MAPK-MK2 pathway thus appears to have extremely complex effects on TTP. Via the regulation of mRNA stability, protein stability and localization it promotes the accumulation of cytoplasmic TTP. However this form of TTP is phosphorylated, inactive, possibly sequestered. The cell is therefore poised to rapidly degrade target mRNAs when the activity of MK2 declines and the kinase-phosphatase equilibrium shifts towards TTP dephosphorylation and activation. At the same time TTP protein becomes susceptible to proteasome-mediated destruction. An intriguing finding that merits further investigation is that the degradation of TTP target mRNAs appears to be somehow coupled to the degradation of TTP protein itself (91).

There are many other interesting questions. For example, does regulation of an mRNA by TTP imply regulation by the p38 MAPK pathway? The majority of known targets of TTP are also post-transcriptionally regulated by the p38 pathway. Novel TTP targets were recently identified by investigation of $TTP^{-/-}$ fibroblasts (114). The most completely characterized of these novel targets was Ier3 (immediate early response 3), which was elsewhere shown to be stabilized in a p38-dependent manner in response to Herpes simplex virus infection (162). It is not yet known whether other recently-identified targets of TTP are post-transcriptionally regulated by p38 MAPK. The question can be put another way: are all genes that are post-transcriptionally regulated by p38 MAPK targets of TTP? This is an important issue, in view of alternative mechanisms of mRNA stabilization by the p38 pathway discussed below. An informative approach might be to ask whether post-transcriptional regulation by p38 MAPK is impaired in non-myeloid cells (for example muscle cells) derived from $TTP^{-/-}$ mice.

A very important question is what the MK2-mediated TTP phosphorylation does if it does not impair RNA binding. An obvious hypothesis is that it blocks the interaction of TTP with one or more of the components of the mRNA decay machinery, but this has not been demonstrated. The many sites of phosphorylation of TTP suggest that it may serve as a target of post-transcriptional regulation by other kinases. Regulation of TTP function through direct phosphorylation by p38 MAPK itself cannot yet be ruled out. According to recent reports the mRNA destabilizing function of TTP could be impaired through activation of the ERK pathway (91, 163). In one case inhibition of both ERK and p38 MAPK was required for prevention of TTP-mediated mRNA decay (91).

Intriguingly, ERK and p38 MAPK pathways also cooperated to regulate the stability of TTP protein (111). Although ERK is known to phosphorylate TTP (147, 152, 153), sites of phosphorylation remain to be identified. Until this is done the nature of the convergence of ERK and p38 MAPK pathways on TTP cannot be elucidated.

4.2. HuR

HuR is the only widely-expressed member of the mammalian ELAV family of RNA binding proteins, the others being restricted to neuronal cells (164). HuR is chiefly localized in the nucleus but, like TTP and many other RNA binding proteins, has the capacity to shuttle between nucleus and cytoplasm. It is clearly an mRNA stabilizing factor that binds to AREs, but it also recognizes other U-rich sequences (165). Consistent with its rather relaxed binding specificity, HuR has been implicated in the post-transcriptional control of many genes (164, 166-168). Amongst these are several genes involved in the regulation of apoptosis, therefore HuR appears to be a key coordinator of a pro-survival program (168). Like the *Drosophila melanogaster* orthologue ELAV, HuR is probably essential for cell survival and proliferation, and no mammalian knockout has yet been described. It is thought to be involved in the assembly of ribonucleoprotein complexes in the nucleus and their export to the cytoplasm as well as subsequent cytoplasmic events. Manipulation of cellular HuR levels may perturb early post-transcriptional events, therefore experiments involving overexpression or knockdown by RNA interference need to be interpreted with caution.

In many cancers, increased cytoplasmic expression of HuR has been linked to poor prognosis and elevated expression of pro-survival genes, in particular COX-2 (33, 167, 169, 170). Cytoplasmic accumulation of HuR is induced by several stimuli, including pro-inflammatory cytokines, ultraviolet light, T cell activation and heat shock. In many cases mRNA stabilization and cytoplasmic accumulation were both prevented by p38 MAPK inhibitors (171-176). It has therefore been suggested that p38 stabilizes target mRNAs by promoting relocalization of the stabilizing factor HuR to the cytoplasm.

We raise a number of concerns about this hypothesis. Whilst p38 MAPK is thought to regulate mRNA deadenylation (67), HuR exerts its stabilizing effect by blocking the degradation of the mRNA body, not deadenylation (176-178). Detailed analysis of COX-2 and IL-8 AREs showed that HuR binding and p38-regulated mRNA stability did not have the same sequence requirements (87, 88). Stimulation of T cells through CD3 induced relocalization of HuR from the nucleus to the cytoplasm but did not stabilize IL-2 mRNA. Costimulation through CD3 and CD28 stabilized IL-2 mRNA but did not further increase cytoplasmic levels of HuR, therefore changes in mRNA stability can be uncoupled from changes in HuR localization (179). Stabilization of mRNA by the p38 MAPK pathway can occur within less than an hour. In many of the cases that have been described, it is not clear that relocalization of HuR to the cytoplasm occurs with similar rapidity. HuR activity and/or localization are regulated directly or indirectly by the checkpoint kinase Chk2, the AMP-regulated kinase and protein kinase C (180-183). However, there is so far no mechanistic explanation for effects of the p38 MAPK pathway on HuR, through phosphorylation of HuR itself or the proteins that control its localization. Until such a link is found it remains possible that relocalization of a small fraction of cellular HuR from the nucleus to the cytoplasm does not have a direct causal role in p38-mediated mRNA stabilization. For example, assume that HuR is required for the export of several mRNAs from the nucleus, and remains associated with those mRNAs throughout their cytoplasmic life-span. The p38-mediated stabilization of a subset of those mRNAs might then lead to, rather than be caused by, an increase in cytoplasmic levels of HuR. Pending the description of a more direct link between HuR and p38 MAPK, this is offered as an alternative hypothesis.

4.3. KSRP

KH-domain splicing regulatory protein (KSRP) belongs to a small family of proteins, members of which have been implicated in the regulation of transcription, mRNA splicing, editing and localization. A recent addition to this list is the regulation of mRNA turnover. KSRP interacts with the exosome and other decay components *in vivo* (13, 16, 18). Depletion of KSRP inhibited the decay of ARE-containing reporter mRNAs *in vitro* and *in vivo* (13), and tethering of KSRP to reporter transcripts promoted their decay (16). KSRP is involved in post-transcriptional regulation by two distinct signaling pathways, the PI3K and p38 MAPK pathways (184-187).

The p38 MAPK pathway controls terminal differentiation of muscle cells by regulating expression of the transcription factor myogenin and the cyclin-dependent kinase inhibitor $p21^{waf/cip}$, amongst several other genes (46). Myogenin and p21 mRNAs are destabilized by KSRP. Under differentiating conditions p38 MAPK is activated, phosphorylates KSRP at threonine 692, inhibits its interaction with RNA and consequently stabilizes myogenin and p21 mRNAs (186). Ten transcripts were found to bind to KSRP in HeLa cells, and to be upregulated and stabilized when KSRP was depleted by RNA interference (187). Amongst these targets, COX-2, CSF2, CXCL2, CXCL3, IL-6 and IL-8 are already known to be post-transcriptionally regulated by the p38 MAPK pathway (Table 1). KSRP is not phosphorylated by MK2 and does not mediate regulation of mRNA stability by MK2 (186, 187). Therefore, two pathways are suggested to exist for the stabilization of target transcripts by the p38 MAPK pathway, one involving the phosphorylation and inactivation of KSRP by p38 itself, the other involving phosphorylation and inactivation of TTP by MK2 (187). It remains to be resolved whether KSRP and TTP function separately or cooperate to modulate mRNA stability in response to p38 MAPK.

The RNA binding specificity of KSRP has not been characterized in detail. Considerable structural flexibility of KSRP protein is thought to underlie its capacity to recognize many different sequence elements

and participate in distinct post-transcriptional processes (188). The two related proteins FBP1 (Far upstream sequence element Binding Protein 1) and FBP3 are 58% and 40% identical to KSRP, but share strongest homology within the KH domains that mediate RNA binding (Figure 3). FBP1 was identified as a HeLa cell protein interacting with the COX-2 ARE (88), and all three family members were identified by affinity purification of proteins recognizing the TNF ARE (89). The site of phosphorylation of KSRP by p38 MAPK is moderately well conserved in FBP1 but not FBP3 (Figure 3). However, it is not known whether FBP1 or FBP3 contributes to ARE-dependent and/or p38-regulated mRNA degradation. KSRP, at least, appears to be a p38-sensitive effector of mRNA decay, but it is unclear whether the specificity of gene regulation by the p38 MAPK pathway can be accounted for by KSRP alone. Possibly the recruitment of KSRP to target transcripts is influenced by other RNA binding proteins that have greater sequence specificity.

4.4. The AUF family

AUF1 was amongst the first ARE-binding proteins to be recognized (2, 3, 189). TNF and IL-1β mRNAs were unusually stable in macrophages derived from an $AUF1^{-/-}$ mouse, the corresponding proteins were overexpressed in response to LPS, and $AUF1^{-/-}$ mice were highly susceptible to lethal endotoxic shock (190). AUF1 is therefore a critical negative regulator of innate immune responses. Four isoforms of AUF1, ranging from 37 kD to 45 kD in molecular mass, are generated by alternative splicing of the primary transcript (Figure 3). Although AUF1 is generally thought of as an mRNA destabilizing factor, it may under some circumstances exert the opposite effect. The AUF1 p37 isoform interacts with the exosome and is the principal destabilizing isoform (18, 191, 192). Post-transcriptional outcomes may depend on the relative levels of expression and subcellular localizations of the four isoforms (193-195). Databases contain a number of proteins closely related to AUF1. One of these, AUF2 (Figure 3), shows strong similarity with AUF1 in terms of its genomic organization, alternative splicing, RNA binding specificity and function (196). AUF2 and other related proteins have been little studied in the context of mRNA stability. It is not clear whether the members of this family have distinct functions or patterns of expression.

MAPKs phosphorylate serine and threonine residues followed by proline residues. Certain phosphorylated Ser-Pro and Thr-Pro sites are recognized by the peptidyl isomerase Pin1, which catalyzes *cis-trans* isomerization about the proline peptide bond, and thus brings about signaling-dependent changes in protein structure and function (197, 198). Pin1 was associated with AUF1 *in vivo*. Inhibition of Pin1 activity decreased the stability of CSF2 mRNA and increased its association with AUF1 (192, 199). These observations are consistent with a model in which phosphorylation of AUF1 converts it into a substrate for Pin1, isomerization of AUF1 inhibits its interaction with CSF2 mRNA and results in stabilization of that transcript.

The ERK pathway controls CSF2 mRNA stability (200) and has been tentatively linked to the Pin1-mediated modulation of mRNA stability (192, 199). However, the p45 isoform of AUF1 contains only three potential sites of phosphorylation by proline-directed kinases, only one of which (S83) has been shown to be phosphorylated *in vivo*. Glycogen synthase kinase 3β rather than ERK was implicated in the phosphorylation of S83; stimulation of the myeloid cell line THP-1 with PMA (a classical activator of the ERK pathway) resulted in loss rather than gain of phosphorylation of S83; and the phosphorylation of this site did not appear to influence affinity for an ARE substrate (201, 202). Furthermore S83 is encoded by exon 2 and is therefore not present in the p37 isoform of AUF1 that is considered the main effector of mRNA degradation. Although Pin1 appears to play a role in the regulation of mRNA stability, it remains to be demonstrated conclusively that AUF1 is the principal target, and the connection with ERK or other MAPK pathways remains to be established.

4.5. Other mediators of post-transcriptional regulation by MAPKs

Heterogeneous nuclear ribonucleoprotein (hnRNP) A_0 (89) and poly (A) binding protein (203) were independently identified as ARE-binding proteins that could be phosphorylated by MK2. In both cases the relevance of such phosphorylation to p38-mediated post-transcriptional regulation remains to be demonstrated.

Translation and turnover of mRNAs are regulated not only by sequence-specific RNA binding proteins but also by short non-coding RNAs known as micro RNAs or miRNAs. Interactions between miRNAs and mRNAs are nucleated by base-pairing between the seven nucleotide "seed region" of the miRNA and a complementary sequence of the target mRNA, most often within the 3' UTR. As described in recent reviews (204-207), miRNAs are now believed to target approximately 30% of eukaryotic protein-coding mRNAs, and to contribute to the regulation of many biological phenomena. At least in part, ARE-dependent and miRNA-mediated post-transcriptional regulation share a subcellular location, the processing body (5-7). There are several possible mechanisms of crosstalk between the two post-transcriptional mechanisms, a few of which have been described in recent publications. **1)** Biogenesis of miRNAs may be regulated by MAPKs at the level of transcription or processing of the precursor RNA. For example expression of miR-155 in response to immune or inflammatory activation is dependent on JNK and/or ERK pathways (208, 209). **2)** Protein components of the miRNA-mediated silencing machinery could be phosphorylated and regulated by MAPK pathways. To our knowledge this has not yet been reported. **3)** miRNAs could participate in the regulation of mRNA stability or translation by sequence-specific RNA binding proteins. The miRNA miR-16 and RNA-induced silencing complex (RISC) were implicated in the regulation of mRNA stability by TTP (210). Curiously, it is not the seed region of miR-16 that is complementary to the ARE core sequence AUUUA, as might be expected for a conserved mechanism of ARE-dependent control. It is also unclear whether the

simultaneous binding of a complementary miRNA and RISC proteins could be consistent with the direct, high affinity interaction of TTP with an RNA substrate. **4)** If miRNAs and RNA-binding proteins recognize identical or overlapping sequences, then MAPK-mediated regulation of protein binding could indirectly influence the miRNA pathway. Conversely, changes in expression of miRNAs could antagonize or augment post-transcriptional regulation by RNA-binding proteins (207). These possibilities have not yet been explored in detail.

5. SUMMARY AND PERSPECTIVE

The study of stimulus-dependent modulation of mRNA stability is relatively new. Although significant advances have been made during the last few years, several major challenges remain. This review has focussed on ARE-binding proteins, but proteins with quite different RNA-binding specificities are becoming recognized as mediators of signal-dependent changes in the translation or degradation of mRNA. It is still not well understood how the primary sequence and secondary structure of an endogenous mRNA determines its interactions with all of these proteins *in vivo*, and how such interactions permit signaling pathways to exert tight control over specific subsets of transcripts. Even amongst well-known and much-studied regulators of mRNA stability, it is unclear how much functional redundancy exists between closely related family members. Although certain important phosphorylation events have been identified, we do not yet know what these phosphorylations mean in terms of the localization of target mRNAs and their interactions with the cellular mRNA degradation machinery. We have described some processes involved in the signal-dependent stabilization of mRNAs. The reverse phenomenon, signal-dependent mRNA destabilization, may be equally important but has not yet been studied in detail. Finally, an area of interest for future research will be the convergence of post-transcriptional mechanisms that depend on sequence-specific protein-RNA or RNA-RNA interactions, and the impact of MAPK signalling on the interactions of the two distinct machineries.

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Abbreviations: ARE, adenine/uridine-rich element; AREBP, ARE-binding protein; AUF, ARE/poly (U)-binding degradation factor; BRF, butyrate response factor; Chk, checkpoint kinase; COX-2, cyclooxygenase 2; CSF, colony stimulating factor; CXCL, chemokine CXC motif ligand; Dcp, decapping protein; ELAV, embryonic lethal abnormal vision; ERK, extracellular signal-regulated kinase; FBP, far upstream sequence element binding protein; FXR1P, fragile X-related protein 1; hnRNP, heterogeneous ribonucleoprotein; HuR, human antigen R; IL, interleukin; iNOS, inducible nitric oxide synthase; JNK, c-Jun N-terminal kinase;JRE, JNK response element; KH, hnRNP K homology domain; KSRP, KH domain splicing regulatory protein; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MK, MAPK-activated kinase; MKK, MAPK kinase; Pin1, protein interacting with NIMA (never in mitosis A) 1; PMA, phorbol-12-myristate-13-acetate; RRM, RNA recognition motif; TIA-1, T cell-restricted intracellular antigen 1; TIAR, TIA-1-related protein; TNF, tumor necrosis factor; TTP, tristetraprolin; UTR, untranslated region; VEGF, vascular endothelial growth factor; YB-1, Y-box binding factor 1; ZFD, zinc finger domain; ZFP36, zinc finger protein of 36 kD; ZFP36L, ZFP36-like protein

Key Words: Adenylate/Uridylate-Rich Element, Auf, ERK, HuR, JNK, KSRP, mitogen-activated protein kinase, mRNA stability, mRNA translation, p38 MAPK, Post-transcriptional regulation, processing body, Protein Phosphorylation, Tristetraprolin, Cytokine Production, Inflammation, Review

Send correspondence to: Andrew R. Clark, Kennedy Institute of Rheumatology Division, Imperial College London, 1 Aspenlea Road, Hammersmith, London W6 8LH, UK, Tel: 0208 383 4430, Fax: 0208 383 4496, E-mail: andy.clark@imperial.ac.uk

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