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Control of mRNA stability by SAPKs

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Abstract

Control of mRNA turnover is an essential step in the regulation of gene expression in eukaryotes. The concerted action of many enzymes regulates the way each mRNA is degraded. Moreover, the degradation of each mRNA is influenced by the environment surrounding the cell. The connection between the environment and changes in the half-lives of mRNAs is regulated by the activity of stress activated MAP kinases (SAPKs) and their substrates. Here we will describe some of those mechanisms, and how SAPKs regulate mRNA stability in eukaryotic cells.

1. Introduction

Stress activated MAP kinases (SAPKs) are kinases activated in response to external stimuli, like stress, hormones, growth factors, etc. There are two families of SAPKs: the c-Jun N-terminal kinases (JNKs) and the p38 kinases. After activation, they coordinate the activation of gene transcription, protein synthesis, cell cycle machinery, cell death, and differentiation, exerting a profound effect in many physiological processes including cell proliferation, inflammation and development (Kyriakis and Avruch 2001). SAPKs are highly conserved in eukaryotes from yeast to human (e.g. mammalian p38, p38-like *S. cerevisiae* Hog1 and *S. pombe* Spc1/Sty1), and because of their importance in cell physiology and disease, they are the subject of intense study.

One of the main functions of SAPKs is the regulation of transcription factors that bind DNA promoters and regulate transcription of different genes. This regulation is achieved through the phosphorylation of transcription factors like ATF2 or c-Jun (Kyriakis and Avruch 2001). However, it is becoming clear that there is another important function of SAPKs that contributes to the correct and timely expression of genes: the control of mRNA stability. Changes in turnover rates of individual mRNAs have great effects in their steady-state levels (Ross 1995; Caponigro and Parker 1996; Wilusz et al. 2001). The advantages of this additional level of regulation are several:

1. Speed: translation and degradation occur with pre-existing mRNAs, saving time in the production of additional mRNAs when necessary, or eliminating mRNAs when the translational machinery needs to be dedicated to other functions.
2. Economy: for similar reasons, stabilization of mRNAs can save precious energy used in transcription, giving an important advantage to the always energy-efficient cell machinery.
3. Control: control of mRNA stability is an additional layer of post-transcriptional regulation that helps to finely adjust the appropriate levels of each mRNA to the environmental conditions.

We are going to discuss some of the mechanisms that control mRNA decay and how SAPKS relate to them.

2. Eukaryotic mRNA turnover

2.1. Proteins involved

Through the study of yeast and mammals, two general pathways of mRNA decay have been identified in eukaryotic cells (Parker and Song 2004)(Figure 1). In the first pathway, the mRNA poly(A) tail is first shortened by mRNA deadenylases. After deadenylation, a decapping enzyme formed by Dcp1 and Dcp2, removes the cap structure in 5', allowing the 5'-3' digestion of the mRNA by Xrn1 exonuclease (Parker and Song 2004). In the second mechanism, deadenylation is followed by 3'-5' degradation of the mRNA by the cytoplasmic exosome, a multisubunit complex formed by many exonucleases (Anderson and Parker 1998; Chen et al. 2001; Wang and Kiledjian 2001; Mukherjee et al. 2002).

There are other pathways of mRNA degradation that are more specialized:

- a. Nuclear degradation of pre-mRNAs that failed to complete processing (Moore 2002).
- b. Degradation of mRNAs with early stop codons in a process referred to as nonsense-mediated decay (NMD). Those mRNAs are degraded by decapping independent of deadenylation or by accelerated 3'-5' exonucleolytic digestion (Muhlrad and Parker 1994; Cao and Parker 2003; Lejeune et al. 2003; Mitchell and Tollervey 2003; Takahashi et al. 2003).
- c. mRNAs lacking stop codon are degraded in a processes named non-stop decay (NSD), by the cytoplasmic exosome (Frischmeyer et al. 2002; van Hoof et al. 2002).

As mentioned above, the first step in the general degradation of mRNA in eukaryotes is deadenylation. At least three different complexes with deadenylation capacity have been identified in eukaryotes: the Ccr4/Pop2 complex (Tucker et al. 2001), the Pan2/Pan3 (PAN) complex (Tucker et al. 2001), and poly(A)-specific exonuclease referred to as PARN (Astrom et al. 1992; Korner and Wahle 1997). In mammalian cells, PARN possesses the major deadenylase activity in vitro (Gao et al. 2000). The poly(A)-binding protein (Pab1) can have opposing effects on the different deadenylating activities, being able to inhibit Ccr4/Pop2 and PARN activity and stimulating PAN. As proposed by Parker and Song (Parker and Song 2004), the composition of the mRNA-protein complex (mRNP) would have important implications for the regulation of mRNA turnover. First, the changes in mRNP composition will alter the susceptibility to different deadenylases. Second, the alteration of one deadenylase would affect a specific set of transcripts. Third, mRNA binding proteins could function by attracting or repelling deadenylase activities to the 3' end of the mRNA.

2.2. Localization

Several studies have shown that mRNA turnover could take place in cytoplasmic bodies. In yeast, many enzymes involved in mRNA degradation like decapping enzymes or exonucleases have been localized to discrete cytoplasmic bodies, where mRNA degradation intermediates have also been found (Sheth and Parker 2003). A different structure, the stress granules, are also cytoplasmic structures that contain translationally repressed mRNAs and mRNAs targeted for degradation (Kedersha and Anderson 2002; Anderson and Kedersha 2006). They may function as a triage system to select mRNAs that need to be translated or degraded, depending of the physiological conditions of the cell.

3. mRNA *cis* acting elements

The decay rates of specific mRNAs can be determined by their sequence elements. The best-studied are AU-rich elements (AREs) which are generally found in the 3' untranslated region (UTR) of mRNAs. AREs modulate stability at the level of deadenylation, decapping or 3'-5' degradation, and can also control translational efficiency (Shaw and Kamen 1986; Chen and Shyu 1995; Bakheet et al. 2001; Wilusz and Wilusz 2004). Proteins that associate with these AREs can either enhance or inhibit mRNA decay rates. Several of these proteins have been described, such as AUF1, Tristetraprolin (TTP), HuR, KSRP, NF90 and TIA-1 (Wilusz and Wilusz 2004). They belong to different protein families, they have different effects on mRNA stability (stabilizing or destabilizing) and modulate different aspects of mRNA metabolism like deadenylation, exosome binding or decapping.

AU-binding proteins recruit the exosome to degrade ARE-containing mRNAs (Chen et al. 2001). Regulated ARE-mediated mRNA decay is also conserved in *Saccharomyces cerevisiae* (Vasudevan and Peltz 2001), and possibly in other eukaryotic microorganisms, opening the possibility of studying these processes in model organisms.

Although the exosome does not exhibit ARE-binding activity, it is recruited to ARE-RNAs through interactions with several ARE-binding proteins such as KSRP and TTP, which in turn recruit the exosome to affect 3'-5' mRNA degradation. ARE-mediated mRNA stability is also regulated by microRNAs in mammalian cells (Jing et al. 2005).

4. Control of mRNA stability by SAPKs

Mammalian SAPKs (JNK and p38) regulate mRNA stability. Stabilization of Interleukin-2 mRNA by the c-Jun NH2-Terminal Kinase Pathway (Chen et al. 1998). The main target of p38 MAP kinase is the kinase MK2, and this signaling pathway regulates the stability and translation of tumor necrosis factor (TNF) and IL-6 mRNAs through a process that involves the AU-rich elements in the 3' UTR of these mRNAs (Kotlyarov et al. 1999; Neininger et al. 2002). Microarray experiments demonstrated that many ARE-containing mRNAs are regulated by p38 activity, but many others are regulated independently of p38 (Frevel et al. 2003).

SAPK p38 signals to cytokine induced mRNA stabilization via MK2 and AU-rich elements (Winzen et al. 1999); it also stabilizes mRNA that contain cyclooxygenase-2 and TNF AREs by inhibiting deadenylation (Dean et al. 2003) and has been found to regulate both the translation and the stability of inflammatory mRNAs. The mRNAs regulated by p38 share common AU-rich elements (ARE) present in their 3'-untranslated regions. AREs act as mRNA instability determinants but also confer stabilisation of the mRNA by the p38 pathway. In recent years, AREs have shown to be binding sites for numerous proteins as mentioned before. However, it is unclear which protein is responsible for mRNA stabilisation by p38 (Dean et al. 2004).

4.1. RNA binding proteins involved in SAPK regulation of mRNA stability

4.1.1. Csx1—*Schizosaccharomyces pombe* Csx1 is a protein with three RNA recognition motifs (RRMs). Under oxidative stress, Csx1 is able to stabilize the mRNA encoding the transcription factor Atf1, being the *csx1Δ* cells sensitive to oxidation. This regulation of Atf1 mRNA half-life is specific of oxidative stress and it is not produced under other types of insult. The absence of Csx1 protein produces a decrease in Atf1 mRNA that, in turn, affect the expression of multiple mRNAs necessary for the correct response to oxidation in fission yeast (Rodríguez-Gabriel et al. 2003).

Csx1 binds to Atf1 mRNA and regulates its turnover rate, and this seems to be the way Csx1 regulates its half-life. Under oxidative stress, Csx1 is phosphorylated dependent on the activity of the p38-like kinase Spc1/Sty1, and correlating with the stabilization of Atf1 mRNA. However, the relationship between this phosphorylation and Csx1 function is unclear (Rodríguez-Gabriel et al. 2003).

Two other RRM-containing proteins have been involved in the regulation of Atf1 mRNA stability in response to oxidative stress in *S. pombe*: Cip1 and Cip2 (Csx1 Interacting Protein 1 and 2). These two proteins interact with Csx1 protein. Elimination of any of them is able to rescue the sensitivity of *csx1Δ* cells to oxidation. Moreover, the absence of Cip1 or Cip2 can override the rapid disappearance of Atf1 mRNA in *csx1Δ* cells and re-establish the correct expression of many of the Csx1-regulated mRNAs (Martin et al. 2006).

4.1.2. HuR—HuR is a mammalian RNA-binding protein that also has three RRMs. HuR binds to several mRNAs (e.g. those that encode TNF α , ATF3, p21WAF1) through their 3'AREs and helps to stabilize them (Wang et al. 2000; Dean et al. 2001; Giles et al. 2003; Pan et al. 2005; Xu et al. 2005). It has been reported that HuR does not alter accumulation of target mRNAs in the absence of the destabilizing function of tristetraprolin (TTP), indicating the functional relationship between both proteins (Katsanou et al. 2005). The way in which HuR functions is still controversial. Recent reports describe the function of HuR in the derepression of gene expression produced by miRNA binding to 3'UTRs. After HuR action, those mRNAs can be released from P-bodies and translated into proteins in response to stress (Bhattacharyya et al. 2006). In some cases, like urokinase and urokinase receptor mRNAs, the stabilization is linked to cytoplasmic accumulation of HuR induced by activated MK2, joining p38 pathway and mRNA stabilization (Tran et al. 2003).

4.1.3. TTP (Tristetraprolin)—TTP downregulates IL-2 gene expression through ARE-mediated mRNA decay (Ogilvie et al. 2005). It is thought that this regulation is possibly achieved by TTP promoting deadenylation of ARE-containing substrates by PARN (Lai et al. 2003). One of the most interesting effects of TTP is the delay of tumor progression. Tumor suppression can be achieved by interfering with RNA turnover (Stoecklin et al. 2003). However many of the phenotypes related with TTP deficiency are related with its regulation of TNF α mRNA regulation. TTP^{-/-} mice have high levels of TNF α mRNA. These mice suffer cachexia, arthritis, and autoimmunity resulting from TTP deficiency. Many of the phenotypes of TTP^{-/-} mice can be overcome by injection of TNF α antibodies (Taylor et al. 1996). TTP destabilizes TNF α mRNA (Carballo et al. 1998), binding to its AU-rich element and promoting its deadenylation (Lai et al. 1999).

TTP deficient cell lines are less sensitive to p38 inhibitors, indicating a possible role of TTP in p38 pathway (Carballo et al. 2001). However there are other reports indicating that p38 does not alter TTP function (Rigby et al. 2005). Depending of the type of stress, TTP can localize to stress granules, where it could regulate degradation of ARE-containing mRNAs along with other ARE-binding factors as TIA-1 and HuR. TTP becomes activated in a p38 dependent manner, binds to 14-3-3 and is excluded from the stress granules (Stoecklin et al. 2004). Therefore, ARE-containing mRNAs are stabilized. It is thought that exclusion of TTP from the stress granules allows HuR to exert its stabilizing effect.

Mitogen-activated protein kinase p38 controls the expression and posttranslational modification of TTP, regulating TNF α mRNA stability (Mahtani et al. 2001), and cyclin D and myc mRNAs (Marderosian et al. 2006). The abundance of TTP mRNA is regulated by p38 and TTP itself (Tchen et al. 2004).

MK2 regulates TNF mRNA stability and translation mainly by altering TTP expression, stability and binding to AREs (Hitti et al. 2006). MK2 phosphorylates TTP of *in vivo* sites, including Ser178, that is a site required for 14-3-3 binding (Chrestensen et al. 2004). MK2 induced TTP:14-3-3 complexes prevent stress granule association and ARE-mRNA decay (Stoecklin et al. 2004).

4.1.4. AUF1—AUF1 has several isoforms. It facilitates rapid decay of AU-rich mRNAs (Sarkar et al. 2003). It has opposite functions to HuR, and the balance of this two proteins could be important for the regulation of mRNA stability (Lu and Schneider 2004).

4.1.5. NF90—Nuclear export of NF90 is required for interleukin-2 mRNA stabilization (Shim et al. 2002), and it could have overlapping functions with HuR.

4.1.6. RHAU—The RHAU RNA helicase facilitates mRNA deadenylation and decay. It interacts with PARN and exosome and the RNA binding proteins HuR and NFAR1 (Tran et al. 2004).

4.1.7. KSRP—KSRP, a KH domain RNA binding protein, was cloned and purified as a component of a splicing complex (Min et al. 1997). It interacts with ARE, exosome and PARN to promote mRNA decay (Gherzi et al. 2004). In fact, tethering KSRP to mRNAs elicit mRNA decay (Chou et al. 2006). It was recently shown that phosphorylation of KSRP in a p38 dependent manner regulates myogenic transcripts, linking SAPK activity and mRNA stability through this RNA binding protein (Briata et al. 2005).

4.1.8 TIA-1 and TIAR—TIA-1 and TIAR show alternative forms of splicing that present several RNA recognition motifs (Beck et al. 1996). TIAR is essential for primordial germ cell development (Beck et al. 1998), and TIA-1 $-/-$ mice develop mild arthritis, with overproduction of TNF alpha and cyclooxygenase-2 by some cell types (Phillips et al. 2004). Proteins from the TIAR/TIA-1 family bind AREs and can also regulate pre-mRNA splicing (Forch et al. 2000). During stress, TIA-1 shuttles between the cytoplasm and the stress granules, accompanying the recruitment of mRNAs to these granules (Kedersha et al. 2000; Kedersha and Anderson 2002). It seems that the main function of the TIAR/TIA-1 family members is the translational repression of mRNAs in response to stress (Mazan-Mamczarz et al. 2006). Although the relationship of these proteins with SAPKs has not been clearly demonstrated, they seem to work in the same situations and under similar stress conditions, opening the possibility of a biochemical relationship between them.

5 Concluding remarks

The role of SAPK pathways in the regulation of posttranscriptional events, and more specifically of mRNA turnover rates, has been the subject of numerous studies in recent years. The participation of SAPKs (and its substrates) in the regulation of mRNA stability, the importance of RNA binding proteins in this process and the different *cis* elements found in mRNAs (AU-rich elements and others), are well established facts. However, there are still many open questions that lay ahead: how is the combination of RNA binding proteins regulating RNA turnover? How are they regulated? How do they interplay with deadenylation machinery, or exosome, or decapping enzymes? How is everything coordinated to function as a eukaryotic operons (Keene and Tenenbaum 2002)? Is it possible to target those mechanisms for therapeutic approaches? With the current rate of progress we can expect answers to these questions in the not too distant future.

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Figure 1. Main mRNA degradation pathways in eukaryotes

Deadenylation-dependent and deadenylation-independent mechanisms of mRNA decay are depicted with the main enzymes involved.