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Posttranscriptional gene regulation by RNA-binding proteins during oxidative stress: implications for cellular senescence

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Abstract

To respond adequately to oxidative stress, mammalian cells elicit rapid and tightly controlled changes in gene expression patterns. Besides alterations in the subsets of transcribed genes, two posttranscriptional processes prominently influence the oxidant-triggered gene expression programs: mRNA turnover and translation. Here, we review recent progress in our knowledge of the turnover and translation regulatory (TTR) mRNA-binding proteins (RBPs) that influence gene expression in response to oxidative damage. Specifically, we identify oxidant damage-regulated mRNAs that are targets of TTR-RBPs, we review the oxidant-triggered signaling pathways that govern TTR-RBP function, and we examine emerging evidence that TTR-RBP activity is altered with senescence and aging. Given the potent influence of TTR-RBPs upon oxidant-regulated gene expression profiles, we propose that the senescence-associated changes in TTR-RBPs directly contribute to the impaired responses to oxidant damage that characterize cellular senescence and advancing age.

Keywords

mRNA stability; posttranscriptional gene regulation; reactive oxygen species (ROS) signaling pathway; RNA-binding proteins; translational control

Introduction: gene regulation in response to oxidative stress

Organisms in aerobic environments are constantly exposed to reactive oxygen species (ROS), which include oxygen-derived radicals (such as hydroxyl radical) and non-radicals (such as hydrogen peroxide) that originate from both intracellular metabolism and exogenous sources. Although transient changes in the levels of ROS can play important regulatory roles in the cell, exposure to sustained or elevated levels of ROS can surpass the antioxidant defenses of the cell and cause severe damage to nucleic acids, proteins and lipids (Camhi et al., 1995; Sies, 1997). Oxidative stress has been implicated in the development of a broad range of pathological processes, particularly aging-associated conditions, such as neurodegenerative disorders, atherosclerosis, diabetes, arthritis and cancer (Finkel and Holbrook, 2000; Bokov et al., 2004).

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Depending on the type, magnitude and duration, oxidant injury can trigger a wide spectrum of intracellular signaling pathways, many of which integrate the responses to both proliferative agents and stress-causing stimuli (Martindale and Holbrook, 2002). These signaling cascades lead to the activation of effector proteins, such as the mitogen-activated protein kinases (MAPKs) [comprising the extracellular signal-regulated kinases (ERK), the c-Jun N-terminal kinases (JNK) and p38], phosphoinositide 3-kinase (PI3K) and protein kinase B (PKB, also called Akt), phospholipase C γ 1 (PLC- γ 1), protein kinase C (PKC), heat shock proteins (HSPs), ataxia-telangiectasia mutated (ATM) kinase, the cytoplasmic Janus protein tyrosine kinases/signal transducers and activators of transcription (JAK/STATs), the Shc adapter p66^{Shc}, the c-Abl tyrosine kinase and the mammalian target of rapamycin (mTOR); they can also repress other pathways, such as that controlling the AMP-activated protein kinase (AMPK) (Martindale and Holbrook, 2002; Leverage et al., 2003; Lim et al., 2006).

The aforementioned pathways influence the cell's phenotypic response to ROS mainly by implementing changes in the patterns of expressed gene products (Allen and Tresini, 2000). These changes are elicited primarily by transcriptional and posttranscriptional mechanisms. The transcriptional regulation of gene expression by ROS can affect genomic regions through oxidant-induced changes in chromatin metabolism (Johnson and Barton 2007), followed by changes in the activities of transcription factors (TFs) regulated by the aforementioned signaling pathways. Accordingly, MAPK activation culminates in the induction of TFs such as c-Jun, Elk-1, MEF2C and ATF2; the PI3K-Akt pathway regulates TFs such as forkhead (FoxO); the heat shock protein response leads to the activation of heat shock factor (HSF1); activation of the ATM pathway leads to increased p53 function; additional signaling pathways lead to the activation of numerous other transcription factors, notably among them the nuclear factor (NF)- κ B (Morano and Thiele, 1999; Brasier, 2006; Niida and Nakanishi, 2006; Huang and Tindall, 2007; Turjanski et al., 2007).

However, there is increasing appreciation that gene expression patterns in cells responding to oxidative stress and other damaging stimuli are also potently modulated by posttranscriptional events. The posttranscriptional regulation of gene expression by ROS is elicited at many steps along the journey of the mRNA, from its *de novo* synthesis as pre-mRNA until its eventual degradation or translation. Generally speaking, these steps include pre-mRNA splicing and maturation (3' polyadenylation, 5' capping), followed by mRNA export to the cytoplasm, subcytoplasmic transport, turnover and translation (Mitchell and Tollervey, 2000; Orphanides and Reinberg, 2002; Moore, 2005). Two main types of *trans* acting factors which recognize specific *cis* elements (RNA sequences) on the target mRNA have been implicated in the regulation of these steps, RNA-binding proteins (RBPs) and microRNAs (Valencia-Sanchez et al., 2006; Keene, 2007). In the case of ROS-regulated gene expression, the involvement of RBPs has been investigated in significant detail, as described in this review, while studies of the participation of microRNAs have only recently begun (Bhattacharyya et al., 2006; Sunkar et al., 2006).

Together, the ROS-triggered transcriptional and post-transcriptional changes, often working together, will collectively dictate the changes in gene expression profiles. In turn, the altered gene expression programs will decisively influence the overall response of the

cell to the oxidative injury. These responses range from proliferation to growth arrest, from differentiation to immune activation, from apoptosis to senescence. While a detailed analysis of these phenotypic responses is beyond the scope of this review, the various ROS-activated pathways distinctly influence the cellular outcome. ERK activation by ROS typically promotes proliferation, differentiation and survival, while p38 and JNK usually enhance inflammation and apoptosis (Dong et al., 2002; Roux and Blenis, 2004). The ROS-induced PI3K-Akt pathway enhances cell growth and proliferation, at least in part, by activating mTOR (Mamane et al., 2006; Schieke and Finkel, 2006). ROS enhances ATM and ATR function leading to the activation of checkpoint kinases Chk1 and Chk2, which in turn trigger cell cycle arrest and extend the time for DNA repair (Sancar et al., 2004; Manning and Cantley, 2007). Similarly, ROS can elicit signaling events through the endoplasmic reticulum (ER) stress and the PKC signaling pathways, which induce NF- κ B activity and enhance cell survival (Gloire et al., 2006; Wek et al., 2006; Wu, 2006).

Here, we will review our knowledge of the RBPs that influence gene expression in response to oxidants, including *bona fide* ROS (e.g., H₂O₂), stimuli that have an oxidative component [e.g., irradiation with short-wave-length ultraviolet light (UVC)] and agents that can generate oxidative damage [endotoxin (lipopolysaccharide, LPS)]. Our attention will focus on proteins that function as mRNA turnover and translation regulatory RBPs [TTR-RBPs, a term recently introduced to replace former terminologies for this heterogeneous group (Pullmann et al., 2007)], because these two regulatory steps are capable of triggering rapid and robust changes in the patterns of expressed genes following exposure to oxidative stress. We will introduce the main ROS-regulated TTR-RBPs and the mRNAs they bind to and regulate, we will review the ROS-triggered signaling pathways that control TTR-RBP activity, and we will consider the mechanisms whereby aging/senescence can aberrantly affect TTR-RBP function and consequently influence gene expression patterns in response to oxidant damage.

RNA-binding proteins controlling mRNA turnover and translation

Many ROS-regulated mRNAs are the targets of TTR-RBPs, which can positively or negatively alter their half-life and translational status (Table 1). While TTR-RBPs constitute a heterogeneous family of proteins, their functions are tightly interconnected and their posttranscriptional influence on the bound mRNA depends largely on the target mRNA itself. In this regard, different TTR-RBPs with affinity for the same target mRNA can display competitive or cooperative interactions among them, as reported for AUF1 (AU-binding factor 1) and TIAR [related to the T-cell intracellular antigen-1 (TIA-1)], as well as for HuR and AUF1 (Lal et al., 2004; Liao et al., 2007). Some TTR-RBPs can influence several distinct processes, such as mRNA translation and turnover, as described for NF90 and HuR (Xu and Grabowski, 1999; Xu et al., 2000, 2003; Shim et al., 2002; Gorospe, 2003). In addition, some TTR-RBPs can exert a given regulatory role (e.g., mRNA turnover) both positively and negatively [e.g., AUF1 can promote and reduce mRNA stability (Brewer, 1991; Xu et al., 2001)]. Finally, TTR-RBPs can regulate each other's expression levels through binding to cognate mRNAs (Pullmann et al., 2007).

TTR-RBPs promoting mRNA decay

The major TTR-RBPs that have been implicated in accelerating the degradation of bound mRNAs include AUF1 [also termed hnRNP D (heterogeneous nuclear ribonucleoprotein)], TTP (tristetraprolin), BRF1 (butyrate response factor-1) and KSRP (KH domain-containing RBP). Below is a brief review of their influence upon target mRNAs implicated in the cellular ROS response.

AUF1—This TTR-RBP comprises a family of four proteins that arise from alternative splicing (p37, p40, p42, p45) and shuttle between the nucleus and the cytoplasm (Zhang et al., 1993; Laroia et al., 1999; Loflin et al., 1999; Shyu and Wilkinson, 2000; Sarkar et al., 2003a). For most target transcripts studied, AUF1 promotes mRNA decay, as measured using AUF1 knockout mice as well as cultured cells expressing different amounts of AUF1 (Brewer, 1991; Sela-Brown et al., 2000; Sarkar et al., 2003b; Raineri et al., 2004; Lal et al., 2004; Fialcowitz et al., 2005); however, AUF1 was also shown to promote mRNA stabilization and translation in several instances (Sela-Brown et al., 2000; Xu et al., 2001; Raineri et al., 2004; Puig et al., 2005; Liao et al., 2007). A number of AUF1 target mRNAs are regulated by oxidative stress, including those that encode p21, cyclin D1, c-myc, c-fos, granulocyte macrophage colony-stimulating factor (GM-CSF), tumor necrosis factor (TNF)- α , interleukin (IL)-3, parathyroid hormone (PTH), and growth arrest and DNA damage-inducible (GADD)45 α mRNAs (Brewer, 1991; Sela-Brown et al., 2000; Xu et al., 2001; Lal et al., 2004, 2006; Raineri et al., 2004; Fialcowitz et al., 2005); however, for many of them, the involvement of AUF1 in their regulation in response to oxidative damage has not been studied. Only in several cases, AUF1 was specifically linked to the regulation of target mRNA expression under conditions of oxidative damage. For example, in response to treatment with prostaglandin A₂, an agent that triggers oxidative stress, or UVC irradiation, AUF1 was shown to lower the stability of cyclin D1 mRNA (Lin et al., 2000; Lal et al., 2006); similarly, the cellular response to LPS, another trigger of ROS, implicated AUF1 in the degradation of target mRNAs encoding TNF- α , IL-1 β and cyclooxygenase-(COX)-2 (Cok et al., 2004; Lu et al., 2006).

BRF1—This TTR-RBP also promotes mRNA decay, as described for TNF- α and IL-3 (Lai et al., 2001; Stoecklin et al., 2002). Both of these cytokines are regulated by oxidative damage, although the involvement of BRF1 in their ROS-controlled mRNA degradation also awaits experimental testing (Ming et al., 1998).

KSRP—It recruits labile mRNAs to the exosome (described below) in a phosphorylation-dependent manner (Chen et al., 2001; Briata et al., 2005) and was proposed to compete with the binding of TTR-RBPs that promote mRNA stability (e.g., HuR). Several targets of KSRP encode oxidative stress-regulated mRNAs, including c-fos, c-jun, inducible nitric oxide synthase (iNOS), TNF- α and IL-2 (Chen et al., 2001; Gherzi et al., 2004; Linker et al., 2005), but the influence of KSRP on their ROS-regulated expression is also unknown at this time.

TTP—This inducible TTR-RBP is predominantly cytoplasmic (Carballo et al., 1998; Linker et al., 2005) and was shown to promote the decay of target mRNAs in a variety of systems

(Carballo et al., 1997, 2000; Lai et al., 1999, 2000, 2002, 2003; Briata et al., 2005; Linker et al., 2005; Lykke-Andersen and Wagner, 2005; Ogilvie et al., 2005). TTP shares with other TTR-RBPs in their affinity for many ROS-regulated mRNAs, such as GM-CSF, c-fos, TNF- α , COX-2 and IL-3 (Lai et al., 1999, 2000, 2002, 2003; Stoecklin et al., 2000; Chen et al., 2001; Sawaoka et al., 2003; Linker et al., 2005). In one specific example, TTP was implicated in the response to ROS in animals fed high-glucose diets, an intervention that triggered oxidative stress and inflammation; these animals had elevated TTP levels in liver and skeletal muscle, linked to a reduction in TNF- α levels (Stoecklin et al., 2004; Cao et al., 2007).

CUG-BP1—This TTR-RBP binds to the ROS-regulated c-jun mRNA and promotes its deadenylation, thereby reducing its stability (Paillard et al., 2002).

The exact mechanisms of degradation of these mRNAs are not fully understood, but they include the action of at least two cellular structures that break down labile mRNAs, the exosome and processing (P)-bodies, as well as one structure wherein mRNAs appear to be protected from degradation, stress granules. The exosome is a large multi-protein complex implicated in the 3'→5' degradation of labile mRNAs following the recruitment by decay-promoting TTR-RBPs (Chen et al., 2001; Butler, 2002; Mukherjee et al., 2002; Gherzi et al., 2004). For mRNAs recruited to the exosome by TTP and KSRP, the activity of deadenylase [poly(A) ribonuclease] (PARN) is also required for transcript decay, suggesting that TTP and KSRP deliver onto target mRNAs the factors necessary for both deadenylation and exosome-mediated degradation (Lai et al., 2003; Gherzi et al., 2004). P-bodies (PBs) are cytoplasmic structures that contain proteins involved in mRNA decapping and 5'→3' degradation (Ingelfinger et al., 2002; Eystathiou et al., 2003; Cougot et al., 2004; Kedersha et al., 2005). PBs are functionally linked to stress granules (SGs), cytoplasmic foci that form transiently in response to ROS and other damaging agents, and represent sites of translational repression (Kedersha and Anderson 2002). Given that mRNAs can be transported between these two subcytosolic domains, SGs have been proposed to serve as sites of storage of untranslated mRNAs until molecular decisions are made to direct the mRNA to polysomes for translation or to PBs for degradation (Kedersha et al., 2005; Wilczynska et al., 2005). The molecular outcomes involve TTR-RBPs which regulate mRNA turnover (such as TTP, KSRP and HuR), as well as translational regulatory factors (TIA-1, TIAR and HuR, discussed below) (Kedersha and Anderson 2002).

TTR-RBPs inhibiting mRNA decay

Other TTR-RBPs have been shown to increase the half-life of target mRNAs. Generally speaking, they enhance the integrity of bound mRNAs by competing with, and hence preventing the binding of degradation-promoting TTR-RBPs, or by transporting mRNAs to parts of the cell where degradation does not occur.

Hu proteins—Mammalian cells encode four closely related members of the Hu family of TTR-RBPs: the ubiquitous HuR (HuA), and the primarily neuronal HuB (Hel-N1), HuC and HuD. The most extensively studied member of this family, HuR, is predominantly nuclear, but its influence upon the expression of target mRNAs is linked to its localization in the

cytoplasm. Oxidative stress agents, such as H₂O₂, arsenite and UVC potently induce HuR translocation to the cytoplasm, where it functions as a promoter of mRNA stability. HuR stabilizes a vast collection of target mRNAs whose levels are regulated by oxidative stress, such as c-fos, p21, cyclin A2, cyclin B1, cyclin D1, iNOS, GM-CSF, vascular endothelial growth factor (VEGF), sirtuin 1 (SIRT1), TNF- α , bcl-2, mcl-1, COX-2, γ -glutamylcysteine synthetase heavy subunit (γ -GCSH), urokinase plasminogen activator (uPA) and its receptor (uPAR) and IL-3 (Fan and Steitz, 1998; Levy et al., 1998; Peng et al., 1998; Wang et al., 2000a,b; Ming et al., 2001; Chen et al., 2002; Sengupta et al., 2003; Tran et al., 2003; Lal et al., 2004; Song et al., 2005; Abdelmohsen et al., 2007a,b). Treatment with H₂O₂ was shown to enhance the binding of HuR to target mRNAs including p21 and MAPK phosphatase-1 (MKP-1); these effects were linked to the enhanced transcript stability and accumulation after oxidative damage (Wang et al., 2000b; Abdelmohsen et al., 2007a; Kuwano et al., submitted). By contrast, H₂O₂ treatment reduced the binding of HuR to SIRT1, cyclin A2 and cyclin B1 mRNAs (Abdelmohsen et al., 2007a), associated with a reduction in mRNA abundance following treatment with the oxidant.

NF90, α CP1, nucleolin, RNPC1, CUG-BP2 and PAIP2—Other TTR-RBPs have also been shown to stabilize target mRNAs, although their functions are less well understood. Few target mRNAs have been identified in each case, but they include several ROS-regulated transcripts, such as p21, IL-2, p53, tyrosine hydroxylase, bcl-2 and COX-2 mRNAs (Paulding and Czyzyk-Krzeska, 1999; Shim et al., 2002; Mukhopadhyay et al., 2003; Sengupta et al., 2004; Shi et al., 2005; Shu et al., 2006). Whether or not these TTR-RBPs specifically stabilize target mRNAs in response to oxidants also remains to be assessed experimentally.

TTR-RBPs promoting mRNA translation

HuR—In addition to its mRNA-stabilizing effects, HuR has been shown to influence (enhance or reduce) the translation of other target mRNAs. HuR increased the translation of target prothymosin (ProT α) and p53 mRNAs in cells responding to UVC and promoted the translation of the cationic amino acid transporter 1 (CAT-1) mRNA in cells responding to arsenite (Mazan-Mamczarz et al., 2003; Lal et al., 2005; Bhattacharyya et al., 2006). In addition, our unpublished studies point to HuR as a potent mediator of the H₂O₂-induced MKP-1 translation (Kuwano et al., unpublished). The molecular mechanisms whereby HuR promotes the translation of these targets have not been elucidated in detail, although they are linked to increases in HuR cytoplasmic abundance in response to oxidant treatment. Only in one recent example, Bhattacharyya and colleagues demonstrated that HuR promoted the translation of target CAT-1 mRNA in response to arsenite treatment by competing with a microRNA (miR-122) which otherwise blocked CAT-1 translation (Bhattacharyya et al., 2006). Another ROS-regulated gene product, cytochrome *c*, was translationally upregulated by HuR, although this regulation was not tested under conditions of oxidative damage (Kawai et al., 2006).

CUG-BP1—This TTR-RBP promotes the translation of a low molecular weight component of the transcription factor CCAAT/enhancer binding protein β (C/EBP β) and induces the translation of p21 (Timchenko et al., 1999, 2001).

TTR-RBPs inhibiting mRNA translation

TIA-1 and TIAR—Oxidants, such as H₂O₂ and arsenite, as well as stresses with a component of oxidative injury (LPS or UVC) trigger the transient aggregation of TIAR and TIA-1 into SGs. At these cytoplasmic foci, TIA-1 and TIAR are believed to suppress the translation of target mRNAs, including many mRNAs that are regulated by oxidative damage. Binding of TIA-1/TIAR to the mRNAs encoding COX-2, TNF- α , GM-CSF, c-myc, calmodulin 2 (CALM2), small nuclear ribonucleoprotein polypeptide F (SNRPF), caspase 8 (CASP8), eukaryotic translation initiation factor 4A (EIF4A1), eukaryotic translation initiation factor 4E (EIF4E2) and eukaryotic translation elongation factor 1 β 2 (EEF1B2) increased in response to stress stimuli and was linked to a suppression of their translation (Piecyk et al., 2000; Kandasamy et al., 2005; López de Silanes et al., 2005; Mazan-Mamczarz et al., 2006; Kim et al., 2007; Tong et al., 2007). Other times, however, binding was reduced by damaging stimuli, prompting instead a restoration of translation. For example, a UVC-triggered dissociation was reported for TIAR target transcripts [such as the paxillin (PXN), eukaryotic translation initiation factor 5A (EIF5A) and the apoptotic peptidase activating factor 1 (APAF1) mRNAs] bearing a recently identified C-rich motif sequence (Kim et al., 2007). The molecular details of the association of TIA-1/TIAR with target mRNAs remain to be fully elucidated, but they are likely linked to the specific RNA sequences involved (e.g., U-rich or C-rich), as well as to posttranslational modifications leading to the recruitment of TIA-1/TIAR to SGs.

NF90 and HuR—Other translational repressors have also been shown to associate with ROS-regulated mRNAs. HuR was shown to repress the translation of p27, the type-I insulin-like growth factor receptor (IGF-IR), Wnt5a and several immune regulators (Kullmann et al., 2002; Katsanou et al., 2005; Meng et al., 2005; Leandersson et al., 2006), although the specific involvement of ROS in these processes remains unexplored. Recent results from our laboratory implicated the transcriptional repressor NF90 in the suppression of MKP-1 translation in response to H₂O₂ treatment (Kuwano et al., unpublished), as shown in other systems (Xu and Grabowski, 1999; Xu et al., 2000, 2003).

ROS-triggered signaling pathways controlling TTR-RBP function

Given the age-related impairment in the cellular response to ROS and the critical functions of ROS-regulated genes, it is particularly important to discuss the signaling pathways that influence TTR-RBP function. In this section, we will present some specific examples of RNP complexes whose function is influenced by the ROS-triggered signaling cascades, highlighting the signal transduction events that are altered with aging/senescence (Figure 1).

PKC α , Cdk1, AMPK and p38 regulate HuR cytoplasmic levels

As mentioned above, a variety of ROS and ROS-triggering stimuli (H₂O₂, arsenite, UVC) induce the export of nuclear HuR to the cytoplasm (Wang et al., 2000b; Abdelmohsen et al., 2007a). At least four kinases have been implicated in the nuclear export of HuR by ROS-producing agents: AMPK, p38, PKC α and Cdk1 (cyclin-dependent kinase 1 or Cdc2). Treatment with UVC inhibited AMPK, a kinase that phosphorylated importin α 1 and promoted its acetylation, in turn enhancing the nuclear import of HuR (Wang et al.,

2002). Consequently, the UVC-inhibited AMPK led to an increase in cytoplasmic HuR and the stabilization of target mRNAs encoding p21, cyclin A2 and cyclin B1 (Wang et al., 2002). This regulation is particularly relevant to cellular senescence, because AMPK activity increases in senescent cells, as discussed below. Activation of the MAPK p38 in response to oxidants, such as sulindac and taxanes, was also linked to increases in the cytoplasmic localization of HuR (Subbaramaiah et al., 2003; Song et al., 2005), although HuR does not appear to be a direct phosphorylation substrate for p38. The transport proteins that participate in the p38-triggered increase in cytoplasmic HuR also remain to be identified. Other kinases have been shown to regulate HuR function by phosphorylating HuR itself. Treatment with an ATP analog activated PKC α , which phosphorylated HuR at residues S158 and S221, and promoted the export of HuR to the cytoplasm, where its target COX-2 mRNA became more stable (Doller et al., 2007). Whether the elevated ATP levels contributed to the increase in cytoplasmic HuR by concomitantly inhibiting AMPK remains to be examined. Our unpublished studies reveal that HuR is an *in vivo* target of Cdk1. Cdk1 was found to phosphorylate HuR at residue S202 and this modification increased HuR's association with a novel nuclear ligand, 14-3-3 θ . According to our findings, Cdk1 phosphorylated HuR at S202, thereby retaining it in the nucleus in association with 14-3-3 θ and hindering its posttranscriptional function and antiapoptotic influence. UVC treatment inhibits Cdk1, in turn decreasing the levels of phosphorylated HuR and augmenting its abundance in the cytoplasm (Kim et al., unpublished). Not unexpectedly, both PKC α and Cdk1 phosphorylate HuR within its hinge region, either at the HuR nucleocytoplasmic shuttling (HNS) domain (S221) or proximal to it (S202), suggesting that local perturbations in charge or conformation within this region perturbs HuR shuttling and consequently its function.

Chk2 and p38 influence binding of HuR to target mRNAs

Recently, ROS-mediated phosphorylation of HuR was also shown to influence HuR binding to target mRNAs. While H₂O₂ treatment increased the cytoplasmic abundance of HuR, it also promoted the dissociation of HuR from several targets, including the SIRT1 and cyclin D1 mRNAs, which decreased their stability (Abdelmohsen et al., 2007a). The loss of these RNPs was attributed to H₂O₂-mediated activation of Chk2, a kinase that phosphorylates HuR within RRM1 (S88), RRM2 (T118) and between both RRMs (S100). Point mutation of these residues revealed a complex pattern of HuR binding, with S100 appearing important for [HuR-SIRT1 mRNA] dissociation after H₂O₂, but S88 and T118 appeared necessary for efficient binding of other targets (Abdelmohsen et al., 2007a). According to these results, phosphorylation of HuR by Chk2 in response to H₂O₂ treatment influenced HuR binding to target mRNAs. These findings are also potentially relevant to the response of senescent cells to H₂O₂, because Chk2 activity decreased in late-passage fibroblasts (Abdelmohsen et al., 2007a). In addition, the p38-triggered elevation in cytoplasmic HuR levels in response to oxidative stimuli (sulindac, taxanes) was linked to the increased binding of HuR to target COX-2 and γ -GCSH mRNAs (Subbaramaiah et al., 2003; Song et al., 2005). This enhanced association with HuR stabilized the COX-2 and γ -GCSH mRNAs and enhanced protein production (Subbaramaiah et al., 2003; Song et al., 2005).

PI3K and p38 phosphorylate KSRP, inactivating its mRNA decay function

Phosphorylation of KSRP has been linked to an inhibition of its mRNA decay-promoting function by two different mechanisms. PI3K-Akt signaling was recently shown to phosphorylate KSRP at S193. This modification promoted the assembly of KSRP with 14-3-3. The resulting complex could not be recruited to the exosome, resulting in the stabilization of a subset of KSRP target transcripts including the β -catenin mRNA (Gherzi et al., 2006; Ruggiero et al., 2007). KSRP was also shown to be a substrate of phosphorylation by p38 (Briata et al., 2005), a modification that did not affect KSRP's ability to interact with the degradation machinery, but did abrogate the binding of KSRP to target mRNAs, rendering them stable. It is important to note that while PI3K-Akt and p38 are pivotal effectors of the cellular response to ROS, their involvement in KSRP phosphorylation in response to oxidative stress has not been shown experimentally.

MAPKAPK2 (MK2) affects TTP function

Arsenite treatment prevents the TTP-elicited degradation of labile target transcripts (Stoecklin et al., 2004). This inhibitory influence was attributed to the phosphorylation of TTP by MAPKAPK2 (MK2) at S52 and S178, which triggered the association of TTP with 14-3-3. The resulting [TTP-14-3-3] complex was excluded from SGs and the bound mRNAs became stable. A similar mechanism was proposed to mediate the stabilization of TNF- α in response to LPS treatment (Stoecklin et al., 2004).

eIF2 α kinases regulate SGs assembly and TIA-1 and TIAR function

In cells responding to oxidative damage, the function of the translational repressors TIA-1 and TIAR is linked to their ability to recruit target mRNAs into SGs (Kedersha and Anderson, 2002; Stoecklin et al., 2004; Kedersha et al., 2005). In unstressed cells, a preinitiation complex comprising eukaryotic translation initiation factors (eIFs) forms at the 5' end of capped mRNAs and is subsequently displaced upon assembly of the 60S subunit to initiate translation. In cells exposed to damaging stimuli, including oxidants, phosphorylation of eIF2 α by a family of kinases (PKR, PERK, GCN2, HRI) reduces the levels of functional preinitiation complex (Holcik and Sonenberg, 2005). Under these conditions, TIAR and TIA-1 associate with the 40S ribosomal subunit, forming inactive preinitiation complexes that function as translational repressors. The self-aggregating properties of TIA-1 and TIAR further facilitate the accumulation of the non-functional preinitiation complexes into SGs. Because other TTR-RBPs are recruited to SGs, these cytoplasmic foci are believed to function as dynamic sites of mRNA *triage* during stress, wherein the composition of RNP complexes and their subsequent engagement with the translation or degradation machineries are decided (Kedersha and Anderson, 2002; Kedersha et al., 2005). According to this regulatory paradigm, eIF2 α kinases directly influence the stability and/or translation of TIA-target mRNAs, even though TIA proteins are not direct substrates of these kinases.

PKA, GSK3 β and ALK influence AUF1 function

Phosphorylation of p40^{AUF1} was reported to occur at S83 and S87 (Wilson et al., 2003a,b). *In vitro* kinase assays indicated that S87 was phosphorylated by protein kinase A (PKA)

and S83 by glycogen synthase kinase (GSK)3 β (Tolnay et al., 2002). Although these modifications were not studied in cells responding to oxidant damage, they did influence the binding of AUF1 to target mRNAs. More recently, AUF1 was shown to be phosphorylated *in vitro* by the anaplastic lymphoma kinase (ALK) and was found hyperphosphorylated in cells expressing a chimeric protein (nucleophosmin-ALK or NPM-ALK) whose presence is linked to anaplastic large cell lymphoma (Fawal et al., 2006). In this study, AUF1 phosphorylation was further correlated with an increase in the stability of several AUF1 target mRNAs encoding proteins with roles in cell proliferation and survival (Fawal et al., 2006).

Akt affects BRF1 function

BRF1 was shown to be phosphorylated by Akt at S92 and S203. As described for TTP (Stoecklin et al., 2004), phosphorylated BRF1 was still capable of binding to target mRNAs, but formed [BRF1–14–3–3] complexes that could not be recruited to the exosome. Consequently, labile target mRNAs were stabilized following BRF1 phosphorylation (Schmidlin et al., 2004; Benjamin et al., 2006). Further studies showed that BRF1 phosphorylation by Akt rendered BRF1 more stable and increased its association with the cytoskeleton (Benjamin et al., 2006). Despite the involvement of Akt in ROS responses, the influence of oxidants upon the Akt-mediated BRF1 phosphorylation also awaits experimental testing.

ROS-regulated TTR-RBP function influencing immune responses

Among all of the biological processes influenced by post-transcriptional gene regulation, the response to immune stimuli is one of the most extensively studied. Given the well-documented influence of TTR-RBPs on the expression of immune-related factors and the deregulation of immune factors with aging, we will review this particular response in this section. Proinflammatory stimuli, such as LPS, TNF- α and IL-1 are potent generators of ROS, which in turn activate many signaling pathways in various cell types, including monocytes, macrophages and lymphocytes (Kaur et al., 2004; Ryan et al., 2004). Oxidative products can also arise in immune cells through multiple intracellular sources, including xanthine oxidase, the mitochondrial electron transport system, peroxisomes and NADPH oxidase. External and internal triggers of ROS, often functioning jointly, have thus emerged as major regulators of immune responses. ROS trigger many signaling pathways in immune cells, most notably activating MAPK cascades and NF- κ B function (Rincón et al., 2000; Bubici et al., 2006). Below are several specific examples of cytokines and the complexity of their regulation by TTR-RBPs in response to ROS.

TNF- α

One of the most prominent gene products regulated by TTR-RBPs is TNF- α , a key cytokine that regulates the inflammatory response and is implicated in the pathogenesis of chronic inflammatory conditions that are more prevalent with increasing age (Ghezzi and Cerami, 2005). TNF- α expression is tightly controlled by both transcriptional and posttranscriptional processes in myeloid cells and macrophages (Chung et al., 2003; Anderson et al., 2004; Seko et al., 2006). The TNF- α 3' untranslated region (UTR) contains specific instability and translation determinants that mediate its posttranscriptional regulation. Deletion of one

particular sequence, an adenine- and uridine-rich element (ARE) from the mouse TNF- α locus, caused an increase in TNF- α mRNA stability due to a reduction in the decay of the TNF- α mRNA, in turn triggering severe chronic inflammation (Katsanou et al., 2005).

Several kinases and TTR-RBPs implicated in regulating TNF- α expression posttranscriptionally have been identified. In myeloid cells, TNF- α was stabilized when LPS or IL-1 activated p38, which in turn phosphorylated MK2, a kinase that phosphorylated TTP and thereby triggered the formation of [TTP-14-3-3] complexes that rendered the TNF- α mRNA stable (Stoecklin et al., 2004). Similarly, TTP-null mice overexpressed TNF- α protein and mRNA both before stimulation and after LPS treatment (Taylor et al., 1996; Phillips et al., 2004). In a related paradigm, Akt phosphorylated KSRP at S193, creating a binding site for 14-3-3 and hence a [KSRP-14-3-3] complex with impaired ability to carry out exosome-mediated degradation of target transcripts, such as TNF- α mRNA (Gherzi et al., 2006). In a similar example, Akt phosphorylated BRF1 at S92 and S203, thereby increasing the binding of 14-3-3 and suppressing its mRNA decay-promoting function (Schmidlin et al., 2004; Benjamin et al., 2006). The TNF- α ARE is also a target of HuR, which stabilized a reporter transcript containing the TNF- α ARE (Dean et al., 2001). LPS-stimulated macrophages derived from TIA-1^{-/-} mice produced more TNF- α protein than those derived from wild-type mice, an effect that was linked to the ability of TIA-1 to bind to the TNF- α ARE and repress its translation (Piecyk et al., 2000; Phillips et al., 2004).

IL-2

Similar to other cytokine mRNAs, the IL-2 3'UTR contains instability determinants that contribute to its short half-life (30–60 min) in resting T cells. This effect was shown to be mediated, at least in part, by TTP and NF90, which promote IL-2 mRNA decay in HeLa cells and in unstimulated T lymphocytes (Shim et al., 2002; Hau et al., 2007). T cell activation triggered the cytoplasmic export of the predominantly nuclear NF90, a process that rendered the IL-2 mRNA stable (Shim et al., 2002). Pro-inflammatory cytokines (IL-1 and TNF- α), UVC, heat shock and oxidative stress also stabilized the IL-2 mRNA in a p38- and JNK-dependent manner. The regulation mediated by JNK was unique in several respects, including the fact that it relied on a JNK-response element (JRE) in the IL-2 5'UTR, but required elements within the 3'UTR to promote the binding of RBPs nucleolin and YB-1 (Chen et al., 1998, 2000).

IL-3

In mast cells treated with ionomycin, IL-3 mRNA stabilization was also found to be dependent on JNK activity, but unlike IL-2, the stability determinant was in its 3'UTR (Ming et al., 1998). In addition, recent studies showed that the PI3K and p38 pathways independently stabilized IL-3 mRNA in NIH 3T3 cells. Interestingly, HuR functioned in conjunction with p38, but not PI3K, to prevent the destabilizing influence of TTP, indicating that the two RBPs competed in controlling IL-3 mRNA stability (Ming et al., 1998).

IL-8

This cytokine is induced in response to pathologic stresses, such as inflammation, hypoxia and oxidative stress. The IL-8 3'UTR contains several stability determinants and was

demonstrated to be a target of HuR, which enhanced its stability in various cell types and in response to inducers, such as IL-1 β (Nabors et al., 2001; Suswam et al., 2005).

IL-1 β

The IL-1 β mRNA was shown to be stable in serum-free adherent monocytes, but it was unstable in adherent cells growing in complete medium. Injection of AUF1 modified the actin cytoskeleton and stabilized the IL-1 β mRNA (Sirenko et al., 2002). These data further suggest the existence of links between mRNA turnover and cytoskeletal function that regulate adhesion-dependent cytokine gene expression.

Changes in TTR-RBP function during senescence/aging

Despite a growing appreciation for the influence of TTR-RBPs on gene expression profiles, little is known about the changes in TTR-RBP function that occur with senescence and/or aging. These age-related changes have only been studied in some detail for three TTR-RBPs proteins (HuR, AUF1, TTP).

HuR

HuR decreased markedly in senescent (late-passage) populations of human diploid fibroblasts (HDFs), a cultured cell model of aging (Wang et al., 2001, 2003). It was also found to be lower in skin fibroblasts from elderly individuals (Wang et al., 2001). This decrease in whole-cell HuR abundance was responsible, at least in part, for the reduced expression levels of cyclin A2 and cyclin B1, two major regulators of cell cycle progression through the S and G2 phases, respectively (Wang et al., 2000a, 2001). In addition, cytoplasmic HuR levels were proportionately diminished in senescent fibroblasts. This reduction was attributed, at least in part, to the fact that AMP/ATP levels increase in senescent fibroblasts, causing an elevation in AMPK activity that promoted the nuclear import of HuR (Wang et al., 2003, 2004). Our unpublished studies also reveal a diminution in HuR abundance in livers from old rodents and a concomitant increase in phosphorylated T172 in the α 1 subunit of AMPK, the active form of the enzyme (Martindale et al., unpublished).

AUF1

It was also found to be lower in senescent human diploid fibroblasts, both in cytoplasmic and in whole-cell preparations. AUF1 associated with the p16 mRNA and contributed to maintaining a short half-life for this transcript (Wang et al., 2005). Therefore, the decay-promoting influence of AUF1 on p16 mRNA was more pronounced in young (early-passage) fibroblasts, which expressed high AUF1 levels, than in senescent (late-passage) fibroblasts, where AUF1 abundance was markedly reduced. The mechanisms regulating the senescence-associated loss of AUF1 expression were not elucidated, but they were linked to the senescent fibroblast phenotype through AUF1's influence on p16 production.

TTP

By contrast, the levels of TTP were recently shown to be elevated in a mouse model of aging. TTP mRNA and protein levels were constitutively higher in primary B cells obtained

from old mice compared with those obtained from young mice, both before stimulation and after LPS treatment (Frasca et al., 2007). Further analysis revealed that TTP transcription was higher in ‘old’ B cells and TTP activity was constitutively elevated. The latter effect was associated with the reduced p38 activity observed in old B cells, a kinase that had been shown to phosphorylate and thereby inactivate TTP. In turn, old B cells expressing higher levels of active TTP displayed reduced levels and a shorter-lived mRNA encoding E47, a transcription factor involved in class switch in B cells (Frasca et al., 2007).

Summary and perspectives

In closing, our understanding of posttranscriptional gene regulation in all areas of biology has advanced remarkably over the past two decades. Many genes specifically implicated in senescence, aging and age-related conditions are encoded by mRNAs whose stability, translation, or both processes are regulated by TTR-RBPs (Brewer, 2002; Lopez de Silanes et al., 2007; Steinman, 2007). As discussed in this review, TTR-RBPs critically influence the expression of aging/senescence-associated mRNAs in response to cellular oxidative stress. Moreover, the signaling pathways that govern the levels and activity of TTR-RBPs are largely regulated by oxidants and impaired with cellular senescence and advancing age.

However, important gaps remain in our understanding of TTP-RBP-mediated gene regulation by oxidative damage, particularly as it changes with increasing age. It is imperative that we examine systematically the levels of TTR-RBP expression and function during aging/senescence. We must also understand more thoroughly the role of TTR-RBPs in gene regulation by ROS. Finally, we must study how ROS influences gene expression post-transcriptionally in senescence/aging model systems. Only then will we be able to fully recognize and intervene in the physiologic and pathologic changes in gene expression patterns that arise with increasing age.

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References

- Abdelmohsen K, Pullmann R Jr, Lal A, Kim HH, Galban S, Yang X, Blethrow JD, Walker M, Shubert J, Gillespie DA, et al. (2007a). Phosphorylation of HuR by Chk2 regulates SIRT1 expression. *Mol. Cell* 25, 543–557. [PubMed: 17317627]
- Abdelmohsen K, Lal A, Kim HH, and Gorospe M (2007b). Posttranscriptional orchestration of an anti-apoptotic program by HuR. *Cell Cycle* 6, 1288–1292. [PubMed: 17534146]
- Allen RG and Tresini M (2000). Oxidative stress and gene regulation. *Free Radic. Biol. Med.* 28, 463–499. [PubMed: 10699758]
- Anderson P, Phillips K, Stoecklin G, and Kedersha N (2004). Post-transcriptional regulation of proinflammatory proteins. *J. Leukoc. Biol.* 76, 42–47. [PubMed: 15075353]
- Benjamin D, Schmidlin M, Min L, Gross B, and Moroni C (2006). BRF1 protein turnover and mRNA decay activity are regulated by protein kinase B at the same phosphorylation sites. *Mol. Cell. Biol.* 26, 9497–9507. [PubMed: 17030608]
- Bhattacharyya SN, Habermacher R, Martine U, Closs EI, and Filipowicz W (2006). Relief of microRNA-mediated translational repression in human cells subjected to stress. *Cell* 125, 1111–1124. [PubMed: 16777601]

- Bokov A, Chaudhuri A, and Richardson A (2004). The role of oxidative damage and stress in aging. *Mech. Ageing Dev.* 125, 811–826. [PubMed: 15541775]
- Brasier AR (2006). The NF- κ B regulatory network. *Cardiovasc. Toxicol.* 6, 111–130. [PubMed: 17303919]
- Brewer G (1991). An A+U-rich element RNA-binding factor regulates c-myc mRNA stability *in vitro*. *Mol. Cell. Biol.* 11, 2460–2466. [PubMed: 1901943]
- Brewer G (2002). Messenger RNA decay during aging and development. *Ageing Res. Rev.* 1, 607–625. [PubMed: 12208236]
- Briata P, Forcales SV, Ponassi M, Corte G, Chen CY, Karin M, Puri PL, and Gherzi R (2005). p38-dependent phosphorylation of the mRNA decay-promoting factor KSRP controls the stability of select myogenic transcripts. *Mol. Cell* 20, 891–903. [PubMed: 16364914]
- Bubici C, Papa S, Dean K, and Franzoso G (2006). Mutual cross-talk between reactive oxygen species and nuclear factor- κ B: molecular basis and biological significance. *Oncogene* 25, 6731–6748. [PubMed: 17072325]
- Butler JS (2002). The yin and yang of the exosome. *Trends Cell Biol.* 12, 90–96. [PubMed: 11849973]
- Camhi SL, Lee P, and Choi AM (1995). The oxidative stress response. *New Horiz.* 3, 170–182. [PubMed: 7583159]
- Cao H, Kelly MA, Kari F, Dawson HD, Urban JF, Coves S, Roussel AM, and Anderson RA (2007). Green tea increases anti-inflammatory tristetraprolin and decreases pro-inflammatory tumor necrosis factor mRNA levels in rats. *J. Inflamm.* 4, 1.
- Carballo E, Gilkeson GS, and Blackshear PJ (1997). Bone marrow transplantation reproduces the tristetraprolin-deficiency syndrome in recombination activating gene-2 mice. Evidence that monocyte/macrophage progenitors may be responsible for TNF α overproduction. *J. Clin. Invest.* 100, 986–995. [PubMed: 9276715]
- Carballo E, Lai WS, and Blackshear PJ (1998). Feedback inhibition of macrophage tumor necrosis factor- α production by tristetraprolin. *Science* 281, 1001–1005. [PubMed: 9703499]
- Carballo E, Lai WS, and Blackshear PJ (2000). Evidence that tristetraprolin is a physiological regulator of granulocyte-macrophage colony-stimulating factor messenger RNA deadenylation and stability. *Blood* 95, 1891–1899. [PubMed: 10706852]
- Chen CY, Del Gatto-Konczak F, Wu Z, and Karin M (1998). Stabilization of interleukin-2 mRNA by the c-Jun NH2-terminal kinase pathway. *Science* 280, 1945–1949. [PubMed: 9632395]
- Chen CY, Gherzi R, Andersen JS, Gaietta G, Jürchott K, Royer HD, Mann M, and Karin M (2000). Nucleolin and YB-1 are required for JNK-mediated interleukin-2 mRNA stabilization during T-cell activation. *Genes Dev.* 14, 1236–1248. [PubMed: 10817758]
- Chen CY, Gherzi R, Ong SE, Chan EL, Raijmakers R, Puijn GJ, Stoecklin G, Moroni C, Mann M, and Karin M (2001). AU binding proteins recruit the exosome to degrade ARE-containing mRNAs. *Cell* 107, 451–464. [PubMed: 11719186]
- Chen CY, Xu N, and Shyu AB (2002). Highly selective actions of HuR in antagonizing AU-rich element-mediated mRNA destabilization. *Mol. Cell. Biol.* 22, 7268–7278. [PubMed: 12242302]
- Chung YJ, Zhou HR, and Pestka JJ (2003). Transcriptional and posttranscriptional roles for p38 mitogen-activated protein kinase in upregulation of TNF- α expression by deoxy-nivalenol (vomitoxin). *Toxicol. Appl. Pharmacol.* 193, 188–201. [PubMed: 14644621]
- Cok SJ, Acton SJ, Sexton AE, and Morrison AR (2004). Identification of RNA-binding proteins in RAW 264.7 cells that recognize a lipopolysaccharide-responsive element in the 3'-untranslated region of the murine cyclooxygenase-2 mRNA. *J. Biol. Chem.* 279, 8196–8205. [PubMed: 14662769]
- Cougot N, Babajko S, and Seraphin B (2004). Cytoplasmic foci are sites of mRNA decay in human cells. *J. Cell Biol.* 165, 31–40. [PubMed: 15067023]
- Dean JL, Wait R, Mahtani KR, Sully G, Clark AR, and Saklatvala J (2001). The 3' untranslated region of tumor necrosis factor α mRNA is a target of the mRNA-stabilizing factor HuR. *Mol. Cell. Biol.* 21, 721–730. [PubMed: 11154260]
- Doller A, Huwiler A, Müller R, Radeke HH, Pfeilschifter J, and Eberhardt W (2007). Protein kinase C α -dependent phosphorylation of the mRNA-stabilizing factor HuR: implications for

- posttranscriptional regulation of cyclooxygenase-2. *Mol. Biol. Cell* 18, 2137–2148. [PubMed: 17392515]
- Dong C, Davis RJ, and Flavell RA (2002). MAP kinases in the immune response. *Annu. Rev. Immunol.* 20, 55–72. [PubMed: 11861597]
- Eystathiou T, Jakymiw A, Chan EK, Seraphin B, Cougot N, and Fritzler MJ (2003). The GW182 protein colocalizes with mRNA degradation associated proteins hDcp1 and hLSm4 in cytoplasmic GW bodies. *RNA* 9, 1171–1173. [PubMed: 13130130]
- Fan XC and Steitz JA (1998). Overexpression of HuR, a nuclear-cytoplasmic shuttling protein, increases the *in vivo* stability of ARE containing mRNAs. *EMBO J.* 17, 3448–3460. [PubMed: 9628880]
- Fawal M, Armstrong F, Ollier S, Dupont H, Touriol C, Monsarrat B, Delsol G, Payraastre B, and Morello D (2006). A ‘liaison dangereuse’ between AUF1/hnRNPd and the oncogenic tyrosine kinase NPM-ALK. *Blood* 108, 2780–2788. [PubMed: 16835382]
- Fialcowitz EJ, Brewer BY, Keenan BP, and Wilson GM (2005). A hairpin-like structure within an AU-rich mRNA-destabilizing element regulates *trans*-factor binding selectivity and mRNA decay kinetics. *J. Biol. Chem.* 280, 22406–22417. [PubMed: 15809297]
- Finkel T and Holbrook NJ (2000). Oxidants, oxidative stress and the biology of ageing. *Nature* 408, 239–247. [PubMed: 11089981]
- Frasca D, Landin AM, Alvarez JP, Blackshear PJ, Riley RL, and Blomberg BB (2007). Tristetraprolin, a negative regulator of mRNA stability, is increased in old B cells and is involved in the degradation of e47 mRNA. *J. Immunol.* 179, 918–927. [PubMed: 17617583]
- Gherzi R, Lee KY, Briata P, Wegmuller D, Moroni C, Karin M, and Chen CY (2004). A KH-domain RNA-binding protein, KSRP, promotes ARE-directed mRNA turnover by recruiting the degradation machinery. *Mol. Cell* 14, 571–583. [PubMed: 15175153]
- Gherzi R, Trabucchi M, Ponassi M, Ruggiero T, Corte G, Moroni C, Chen CY, Khabar KS, Andersen JS, and Briata P (2006). The RNA-binding protein KSRP promotes decay of β -catenin mRNA and is inactivated by PI3K-AKT signaling. *PLoS Biol.* 5, e5. [PubMed: 17177604]
- Ghezzi P and Cerami A (2005). Tumor necrosis factor as a pharmacological target. *Mol. Biotechnol.* 31, 239–244. [PubMed: 16230774]
- Gloire G, Legrand-Poels S, and Piette J (2006). NF-kappaB activation by reactive oxygen species: fifteen years later. *Biochem. Pharmacol.* 72, 1493–1505. [PubMed: 16723122]
- Gorospe M (2003). HuR in the mammalian genotoxic response: post-transcriptional multitasking. *Cell Cycle* 2, 412–414. [PubMed: 12963828]
- Hau HH, Walsh RJ, Ogilvie RL, Williams DA, Reilly CS, and Bohjanen PR (2007). Tristetraprolin recruits functional mRNA decay complexes to ARE sequences. *J. Cell. Biochem.* 100, 1477–1492. [PubMed: 17133347]
- Holcik M and Sonenberg N (2005). Translational control in stress and apoptosis. *Nat. Rev. Mol. Cell. Biol.* 6, 318–327. [PubMed: 15803138]
- Huang H and Tindall DJ (2007). Dynamic FoxO transcription factors. *J. Cell Sci.* 120, 2479–2487. [PubMed: 17646672]
- Ingelfinger D, Arndt-Jovin DJ, Luhrmann R, and Achsel T (2002). The human LSM1–7 proteins colocalize with the mRNA-degrading enzymes Dcp1/2 and Xrn1 in distinct cytoplasmic foci. *RNA* 8, 1489–1501. [PubMed: 12515382]
- Johnson AB and Barton MC (2007). Hypoxia-induced and stress-specific changes in chromatin structure and function. *Mutat. Res.* 618, 149–162. [PubMed: 17292925]
- Kandasamy K, Joseph K, Subramaniam K, Raymond JR, and Tholanikunnel BG (2005). Translational control of β 2-adrenergic receptor mRNA by T-cell-restricted intracellular antigen-related protein. *J. Biol. Chem.* 280, 1931–1943. [PubMed: 15536087]
- Katsanou V, Papadaki O, Milatos S, Blackshear PJ, Anderson P, Kollias G, and Kontoyiannis DL (2005). HuR as a negative posttranscriptional modulator in inflammation. *Mol. Cell* 19, 777–789. [PubMed: 16168373]
- Kaur J, Dhaunsi GS, and Turner RB (2004). Interleukin-1 and nitric oxide increase NADPH oxidase activity in human coronary artery smooth muscle cells. *Med. Princ. Pract.* 13, 26–29. [PubMed: 14657615]

- Kawai T, Lal A, Yang X, Galban S, Mazan-Mamczarz K, and Gorospe M (2006). Translational control of cytochrome *c* by RNA-binding proteins TIA-1 and HuR. *Mol. Cell. Biol.* 26, 3295–3307. [PubMed: 16581801]
- Kedersha N and Anderson P (2002). Stress granules: sites of mRNA triage that regulate mRNA stability and translatability. *Biochem. Soc. Trans.* 30, 963–969. [PubMed: 12440955]
- Kedersha N, Stoecklin G, Ayodele M, Yacono P, Lykke-Andersen J, Fitzler MJ, Scheuner D, Kaufman RJ, Golan DE and Anderson P (2005). Stress granules and processing bodies are dynamically linked sites of mRNP remodeling. *J. Cell Biol.* 169, 871–884. [PubMed: 15967811]
- Keene JD (2007). RNA regulons: coordination of post-transcriptional events. *Nat. Rev. Genet.* 8, 533–543. [PubMed: 17572691]
- Kim HS, Kuwano Y, Zhan M, Pullmann R Jr, Mazan-Mamczarz K, Li H, Kedersha N, Anderson P, Wilce MCJ, Gorospe M, and Wilce JA (2007). Elucidation of a C-rich signature motif in target mRNAs of RNA-binding protein TIAR. *Mol. Cell. Biol.* 27, 6806–6817. [PubMed: 17682065]
- Kullmann M, Gopfert U, Siewe B, and Hengst L (2002). ELAV/Hu proteins inhibit p27 translation via an IRES element in the p27 5'UTR. *Genes Dev.* 16, 3087–3099. [PubMed: 12464637]
- Lai WS, Carballo E, Strum JR, Kennington EA, Phillips RS, and Blackshear PJ (1999). Evidence that tristetraprolin binds to AU-rich elements and promotes the deadenylation and destabilization of tumor necrosis factor α mRNA. *Mol. Cell. Biol.* 19, 4311–4323. [PubMed: 10330172]
- Lai WS, Carballo E, Thorn JM, Kennington EA, and Blackshear PJ (2000). Interactions of CCCH zinc finger proteins with mRNA. Binding of tristetraprolin-related zinc finger proteins to AU-rich elements and destabilization of mRNA. *J. Biol. Chem.* 275, 17827–17837. [PubMed: 10751406]
- Lai WS and Blackshear PJ (2001). Interactions of CCCH zinc finger proteins with mRNA: tristetraprolin-mediated AU-rich element dependent mRNA degradation can occur in the absence of a poly(A) tail. *J. Biol. Chem.* 276, 23144–23154. [PubMed: 11279239]
- Lai WS, Kennington EA, and Blackshear PJ (2002). Interactions of CCCH zinc finger proteins with mRNA: non-binding tristetraprolin mutants exert an inhibitory effect on degradation of AU-rich element containing mRNAs. *J. Biol. Chem.* 277, 9606–9613. [PubMed: 11782475]
- Lai WS, Kennington EA, and Blackshear PJ (2003). Tristetraprolin and its family members can promote the cell-free deadenylation of AU-rich element-containing mRNAs by poly(A) ribonuclease. *Mol. Cell. Biol.* 23, 3798–3812. [PubMed: 12748283]
- Lal A, Mazan-Mamczarz K, Kawai T, Yang X, Martindale JL, and Gorospe M (2004). Concurrent versus individual binding of HuR and AUF1 to common labile target mRNAs. *EMBO J.* 23, 3092–3102. [PubMed: 15257295]
- Lal A, Kawai T, Yang X, Mazan-Mamczarz K, and Gorospe M (2005). Antiapoptotic function of RNA-binding protein HuR effected through prothymosin α . *EMBO J.* 24, 1852–1862. [PubMed: 15861128]
- Lal A, Abdelmohsen K, Pullmann R, Kawai T, Yang X, Galban S, Brewer G, and Gorospe M (2006). Posttranscriptional derepression of GADD45 α by genotoxic stress. *Mol. Cell* 22, 117–128. [PubMed: 16600875]
- Laroia G, Cuesta R, Brewer G, and Schneider RJ (1999). Control of mRNA decay by heat shock-ubiquitin-proteasome pathway. *Science* 284, 499–502. [PubMed: 10205060]
- Leandersson K, Riesbeck K, and Andersson T (2006). Wnt5a mRNA translation is suppressed by the Elav-like protein HuR in human breast epithelial cells. *Nucleic Acids Res.* 34, 3988–3999. [PubMed: 16914445]
- Leverve XM, Guigas B, Demaille D, Batandier C, Koceir EA, Chauvin C, Fontaine E, and Wiernsperger NF (2003). Mitochondrial metabolism and type-2 diabetes: a specific target of metformin. *Diabetes Metab.* 29, 6S88–6S94. [PubMed: 14502105]
- Levy N, Chung S, Furneaux H, and Levy A (1998). Hypoxic stabilization of vascular endothelial growth factor mRNA by the RNA-binding protein HuR. *J. Biol. Chem.* 273, 6417–6423. [PubMed: 9497373]
- Liao B, Hu Y, and Brewer G (2007). Competitive binding of AUF1 and TIAR to MYC mRNA controls its translation. *Nat. Struct. Mol. Biol.* 14, 511–518. [PubMed: 17486099]
- Lim HY, Bodmer R, and Perrin L (2006). *Drosophila* aging 2005/06. *Exp. Gerontol.* 41, 1213–1216. [PubMed: 17126511]

- Lin S, Wang W, Wilson GM, Yang X, Brewer G, Holbrook NJ, and Gorospe M (2000). Downregulation of cyclin D1 expression by prostaglandin A2 is mediated by enhanced cyclin D1 mRNA turnover. *Mol. Cell. Biol.* 20, 7903–7913. [PubMed: 11027261]
- Linker K, Pautz A, Fechir M, Hubrich T, Greeve J, and Kleinert H (2005). Involvement of KSRP in the post-transcriptional regulation of human iNOS expression-complex interplay of KSRP with TTP and HuR. *Nucleic Acids Res.* 33, 4813–4827. [PubMed: 16126846]
- Loflin P, Chen CY, and Shyu AB (1999). Unraveling a cytoplasmic role for hnRNP D in the in vivo mRNA destabilization directed by the AU-rich element. *Genes Dev.* 13, 1884–1897. [PubMed: 10421639]
- López de Silanes I, Galban S, Martindale JL, Yang X, Mazan-Mamczarz K, Indig FE, Falco G, Zhan M, and Gorospe M (2005). Identification and functional outcome of mRNAs associated with RNA-binding protein TIA-1. *Mol. Cell. Biol.* 25, 9520–9531. [PubMed: 16227602]
- Lopez de Silanes I, Quesada MP, and Esteller M (2007). Aberrant regulation of messenger RNA 3'-untranslated region in human cancer. *Cell Oncol.* 29, 1–17.
- Lu JY, Sadri N, and Schneider RJ (2006). Endotoxic shock in AUF1 knockout mice mediated by failure to degrade pro-inflammatory cytokine mRNAs. *Genes Dev.* 20, 3174–3184. [PubMed: 17085481]
- Lykke-Andersen J and Wagner E (2005). Recruitment and activation of mRNA decay enzymes by two ARE-mediated decay activation domains in the proteins TTP and BRF-1. *Genes Dev.* 19, 351–361. [PubMed: 15687258]
- Mamane Y, Petroulakis E, LeBacquer O, and Sonenberg N (2006). mTOR, translation initiation and cancer. *Oncogene* 25, 6416–6422. [PubMed: 17041626]
- Manning BD and Cantley LC (2007). AKT/PKB signaling: navigating downstream. *Cell* 129, 1261–1274. [PubMed: 17604717]
- Martindale JL and Holbrook NJ (2002). Cellular response to oxidative stress: signaling for suicide and survival. *J. Cell Physiol.* 192, 1–15. [PubMed: 12115731]
- Mazan-Mamczarz K, Galban S, López de Silanes I, Martindale JL, Atasoy U, Keene JD, and Gorospe M (2003). RNA-binding protein HuR enhances p53 translation in response to ultraviolet light irradiation. *Proc. Natl. Acad. Sci. USA* 100, 8354–8359. [PubMed: 12821781]
- Mazan-Mamczarz K, Lal A, Martindale JL, Kawai T, and Gorospe M (2006). Translational repression by RNA-binding protein TIAR. *Mol. Cell. Biol.* 26, 2716–2727. [PubMed: 16537914]
- Meng Z, King PH, Nabors LB, Jackson NL, Chen CY, Emanuel PD, and Blume SW (2005). The ELAV RNA-stability factor HuR binds the 5'-untranslated region of the human IGF-IR transcript and differentially represses cap-dependent and IRES-mediated translation. *Nucleic Acids Res.* 33, 2962–2979. [PubMed: 15914670]
- Ming XF, Kaiser M, and Moroni C (1998). c-jun N-terminal kinase is involved in AUUUA-mediated interleukin-3 mRNA turnover in mast cells. *EMBO J.* 17, 6039–6048. [PubMed: 9774347]
- Ming XF, Stoecklin G, Lu M, Looser R, and Moroni C (2001). Parallel and independent regulation of interleukin-3 mRNA turnover by phosphatidylinositol 3-kinase and p38 mitogen-activated protein kinase. *Mol. Cell. Biol.* 21, 5778–5789. [PubMed: 11486017]
- Mitchell P and Tollervey D (2000). mRNA stability in eukaryotes. *Curr. Opin. Genet. Dev.* 10, 193–198. [PubMed: 10753781]
- Morano KA and Thiele DJ (1999). Heat shock factor function and regulation in response to cellular stress, growth, and differentiation signals. *Gene Expr.* 7, 271–282. [PubMed: 10440228]
- Moore MJ (2005). From birth to death: the complex lives of eukaryotic mRNAs. *Science* 309, 1514–1518. [PubMed: 16141059]
- Mukherjee D, Gao M, O'Connor JP, Raijmakers R, Pruijn GLutz CS, and Wilusz J (2002). The mammalian exosome mediates the efficient degradation of mRNAs that contain AU-rich elements. *EMBO J.* 21, 165–174. [PubMed: 11782436]
- Mukhopadhyay D, Houchen CW, Kennedy S, Dieckgraefe BK, and Anant S (2003). Coupled mRNA stabilization and translational silencing of cyclooxygenase-2 by a novel RNA binding protein, CUGBP2. *Mol. Cell* 11, 113–126. [PubMed: 12535526]
- Nabors LB, Gillespie GY, Harkins L, and King PH (2001). HuR, a RNA stability factor, is expressed in malignant brain tumors and binds to adenine- and uridine-rich elements within the 3' untranslated

- regions of cytokine and angiogenic factor mRNAs. *Cancer Res.* 61, 2154–2161. [PubMed: 11280780]
- Niida H and Nakanishi M (2006). DNA damage checkpoints in mammals. *Mutagenesis* 21, 3–9. [PubMed: 16314342]
- Ogilvie RL, Abelson M, Hau HH, Vlasova I, Blackshear PJ, and Bohjanen PR (2005). Tristetraprolin down-regulates IL-2 gene expression through AU-rich element-mediated mRNA decay. *J. Immunol.* 174, 953–961. [PubMed: 15634918]
- Orphanides G and Reinberg D (2002). A unified theory of gene expression. *Cell* 108, 439–451. [PubMed: 11909516]
- Paillard L, Legagneux V, Maniey D, and Osborne HB (2002). c-Jun ARE targets mRNA deadenylation by an EDEN-BP (embryo deadenylation element-binding protein)-dependent pathway. *J. Biol. Chem.* 277, 3232–3235. [PubMed: 11707455]
- Paulding WR and Czyzyk-Krzeska MF (1999). Regulation of tyrosine hydroxylase mRNA stability by protein-binding, pyrimidine-rich sequence in the 3'-untranslated region. *J. Biol. Chem.* 274, 2532–2538. [PubMed: 9891025]
- Peng SS, Chen CY, Xu N, and Shyu AB (1998). RNA stabilization by the AU-rich element binding protein, HuR, an ELAV protein. *EMBO J.* 17, 3461–3470. [PubMed: 9628881]
- Phillips K, Kedersha N, Shen L, Blackshear PJ, and Anderson P (2004). Arthritis suppressor genes TIA-1 and TTP dampen the expression of tumor necrosis factor α , cyclooxygenase 2, and inflammatory arthritis. *Proc. Natl. Acad. Sci. USA* 101, 2011–2016. [PubMed: 14769925]
- Pieczek M, Wax S, Beck AR, Kedersha N, Gupta M, Maritim B, Chen S, Gueydan C, Kruys V, Streuli M, et al. (2000). TIA-1 is a translational silencer that selectively regulates the expression of TNF- α . *EMBO J.* 19, 4154–4163. [PubMed: 10921895]
- Puig S, Askeland E, and Thiele DJ (2005). Coordinated remodeling of cellular metabolism during iron deficiency through targeted mRNA degradation. *Cell* 120, 99–110. [PubMed: 15652485]
- Pullmann R Jr, Kim HH, Abdelmohsen K, Lal A, Martindale JL, Yang X, and Gorospe M (2007). Analysis of stability and translation regulatory RBP expression through binding to cognate mRNAs. *Mol. Cell. Biol.* 27, 6265–6278. [PubMed: 17620417]
- Raineri I, Wegmueller D, Gross B, Certa U, and Moroni C (2004). Roles of AUF1 isoforms, HuR and BRF1 in ARE-dependent mRNA turnover studied by RNA interference. *Nucleic Acids Res.* 32, 1279–1288. [PubMed: 14976220]
- Rincón M, Flavell RA, and Davis RA (2000). The JNK and P38 MAP kinase signaling pathways in T cell-mediated immune responses. *Free Radic. Biol. Med.* 28, 1328–1337. [PubMed: 10924852]
- Roux PP and Blenis J (2004). ERK and p38 MAPK-activated protein kinases: a family of protein kinases with diverse biological functions. *Microbiol. Mol. Biol. Rev.* 68, 320–344. [PubMed: 15187187]
- Ruggiero T, Trabucchi M, Ponassi M, Corte G, Chen CY, al-Haj L, Khabar KS, Briata P, and Gherzi R (2007). Identification of a set of KSRP target transcripts upregulated by PI3K-AKT signaling. *BMC Mol. Biol.* 8, 28. [PubMed: 17437629]
- Ryan KA, Smith MF Jr, Sanders MK, and Ernst PB (2004). Reactive oxygen and nitrogen species differentially regulate Toll-like receptor 4-mediated activation of NF- κ B and interleukin-8 expression. *Infect. Immun.* 72, 2123–2130. [PubMed: 15039334]
- Sancar A, Lindsey-Boltz LA, Unsal-Kacmaz K, and Linn S (2004). Molecular mechanisms of mammalian DNA repair and the DNA damage checkpoints. *Annu. Rev. Biochem.* 73, 39–85. [PubMed: 15189136]
- Sarkar B, Lu JY, and Schneider RJ (2003a). Nuclear import and export functions in the different isoforms of the AUF1/heterogeneous nuclear ribonucleoprotein protein family. *J. Biol. Chem.* 278, 20700–20707. [PubMed: 12668672]
- Sarkar B, Xi Q, He C, and Schneider RJ (2003b). Selective degradation of AU-rich mRNAs promoted by the p37 AUF1 protein isoform. *Mol. Cell. Biol.* 23, 6685–6693. [PubMed: 12944492]
- Sawaoka H, Dixon DA, Oates JA, and Boutaud O (2003). Tristetraprolin binds to the 3'-untranslated region of cyclooxygenase-2 mRNA. A polyadenylation variant in a cancer cell line lacks the binding site. *J. Biol. Chem.* 278, 13928–13935. [PubMed: 12578839]

- Schieke SM and Finkel T (2006). Mitochondrial signaling, TOR, and life span. *Biol. Chem.* 387, 1357–1361. [PubMed: 17081107]
- Schmidlin M, Lu M, Leuenberger SA, Stoecklin G, Mallaun M, Gross B, Gherzi R, Hess D, Hemmings BA, and Moroni C (2004). The ARE-dependent mRNA-destabilizing activity of BRF1 is regulated by protein kinase B. *EMBO J.* 23, 4760–4769. [PubMed: 15538381]
- Seko Y, Cole S, Kasprzak W, Shapiro BA, and Ragheb JA (2006). The role of cytokine mRNA stability in the pathogenesis of autoimmune disease. *Autoimmun. Rev.* 5, 299–305. [PubMed: 16782553]
- Sela-Brown A, Silver J, Brewer G, and Naveh-Many T (2000). Identification of AUF1 as a parathyroid hormone mRNA 3'-untranslated region-binding protein that determines parathyroid hormone mRNA stability. *J. Biol. Chem.* 275, 7424–7429. [PubMed: 10702317]
- Sengupta S, Jang BC, Wu MT, Paik JH, Furneaux H, and Hla T (2003). The RNA-binding protein HuR regulates the expression of cyclooxygenase-2. *J. Biol. Chem.* 278, 25227–25233. [PubMed: 12704185]
- Sengupta TK, Bandyopadhyay S, Fernandes DJ, and Spicer EK (2004). Identification of nucleolin as an AU-rich element binding protein involved in bcl-2 mRNA stabilization. *J. Biol. Chem.* 279, 10855–10863. [PubMed: 14679209]
- Shi L, Zhao G, Qiu D, Godfrey WR, Vogel H, Rando TA, Hu H, and Kao PN (2005). NF90 regulates cell cycle exit and terminal myogenic differentiation by direct binding to the 3'-untranslated region of MyoD and p21WAF1/CIP1 mRNAs. *J. Biol. Chem.* 280, 18981–18989. [PubMed: 15746098]
- Shim J, Lim HR, Yates J, and Karin M (2002). Nuclear export of NF90 is required for interleukin-2 mRNA stabilization. *Mol. Cell* 10, 1331–1344. [PubMed: 12504009]
- Shu L, Yan W, and Chen X (2006). RNPC1, an RNA-binding protein and a target of the p53 family, is required for maintaining the stability of the basal and stress-induced p21 transcript. *Genes Dev.* 20, 2961–2972. [PubMed: 17050675]
- Shyu AB and Wilkinson MF (2000). The double lives of shuttling mRNA binding proteins. *Cell* 102, 135–138. [PubMed: 10943833]
- Sies H (1997). Oxidative stress: oxidants and antioxidants. *Exp. Physiol.* 82, 291–295. [PubMed: 9129943]
- Sirenko O, Bocker U, Morris JS, Haskill JS, and Watson JM (2002). IL-1 β transcript stability in monocytes is linked to cytoskeletal reorganization and the availability of mRNA degradation factors. *Immunol. Cell Biol.* 80, 328–339. [PubMed: 12121221]
- Song IS, Tatebe S, Dai W, and Kuo MT (2005). Delayed mechanism for induction of gamma-glutamylcysteine synthetase heavy subunit mRNA stability by oxidative stress involving p38 mitogen-activated protein kinase signaling. *J. Biol. Chem.* 280, 28230–28240. [PubMed: 15946948]
- Steinman RA (2007). mRNA stability control: a clandestine force in normal and malignant hematopoiesis. *Leukemia* 21, 1158–1171. [PubMed: 17392821]
- Stoecklin G, Ming XF, Looser R, and Moroni C (2000). Somatic mRNA turnover mutants implicate tristetraprolin in the interleukin-3 mRNA degradation pathway. *Mol. Cell. Biol.* 20, 3753–3763. [PubMed: 10805719]
- Stoecklin G, Colombi M, Raineri I, Leuenberger S, Mallaun M, Schmidlin M, Gross B, Lu M, Kitamura T, and Moroni C (2002). Functional cloning of BRF1, a regulator of ARE-dependent mRNA turnover. *EMBO J.* 21, 4709–4718. [PubMed: 12198173]
- Stoecklin G, Stubbs T, Kedersha N, Wax S, Rigby WF, Blackwell TK, and Anderson P (2004). MK2-induced tristetraprolin:14-3-3 complexes prevent stress granule association and ARE-mRNA decay. *EMBO J.* 23, 1313–1324. [PubMed: 15014438]
- Subbaramaiah KMarmo TP, Dixon DA, and Dannenberg AJ (2003). Regulation of cyclooxygenase-2 mRNA stability by taxanes: evidence for involvement of p38, MAPKAPK-2, and HuR. *J. Biol. Chem.* 278, 37637–37647. [PubMed: 12826679]
- Sunkar R, Kapoor A, and Zhu JK (2006). Posttranscriptional induction of two Cu/Zn superoxide dismutase genes in *Arabidopsis* is mediated by downregulation of miR398 and important for oxidative stress tolerance. *Plant Cell* 18, 2051–2065. [PubMed: 16861386]

- Suswam EA, Nabors LB, Huang Y, Yang X, and King PH (2005). IL-1 β induces stabilization of IL-8 mRNA in malignant breast cancer cells via the 3' untranslated region: involvement of divergent RNA-binding factors HuR, KSRP and TIAR. *Int. J. Cancer* 113, 911–919. [PubMed: 15514971]
- Taylor GA, Carballo E, Lee DM, Lai WS, Thompson MJ, Patel DD, Schenkman DI, Gilkeson GS, Broxmeyer HE, Haynes BF, et al. (1996). A pathogenetic role for TNF- α in the syndrome of cachexia, arthritis, and autoimmunity resulting from tristetraprolin (TTP) deficiency. *Immunity* 4, 445–454. [PubMed: 8630730]
- Timchenko NA, Welm AL, Lu X, and Timchenko LT (1999). CUG repeat binding protein (CUGBP1). interacts with the 5' region of C/EBP β mRNA and regulates translation of C/EBP β isoforms. *Nucleic Acids Res.* 27, 4517–4525. [PubMed: 10536163]
- Timchenko NA, Iakova P, Cai ZJ, Smith JR, and Timchenko LT (2001). Molecular basis for impaired muscle differentiation in myotonic dystrophy. *Mol. Cell. Biol.* 21, 6927–6938. [PubMed: 11564876]
- Tolnay M, Juang Y-T, and Tsokos GC (2002). Protein kinase A enhances, whereas glycogen synthase kinase-3 β inhibits, the activity of the exon 2-encoded transactivator domain of heterogeneous nuclear ribonucleoprotein D in a hierarchical fashion. *Biochem. J.* 363, 127–136. [PubMed: 11903055]
- Tong X, Van Dross RT, Abu-Yousif A, Morrison AR, and Pelling JC (2007). Apigenin prevents UVB-induced cyclooxygenase 2 expression: coupled mRNA stabilization and translational inhibition. *Mol. Cell. Biol.* 27, 283–296. [PubMed: 17074806]
- Tran H, Maurer F, and Nagamine Y (2003). Stabilization of urokinase and urokinase receptor mRNAs by HuR is linked to its cytoplasmic accumulation induced by activated mitogen-activated protein kinase-activated protein kinase 2. *Mol. Cell. Biol.* 23, 7177–7188. [PubMed: 14517288]
- Turjanski AG, Vaqué JP, and Gutkind JS (2007). MAP kinases and the control of nuclear events. *Oncogene* 26, 3240–3253. [PubMed: 17496919]
- Valencia-Sanchez MA, Liu J, Hannon GJ, and Parker R (2006). Control of translation and mRNA degradation by miRNAs and siRNAs. *Genes Dev.* 20, 515–524. [PubMed: 16510870]
- Wang W, Caldwell MC, Lin S, Furneaux H, and Gorospe M (2000a). HuR regulates cyclin A and cyclin B1 mRNA stability during cell proliferation. *EMBO J.* 19, 2340–2350. [PubMed: 10811625]
- Wang W, Furneaux H, Cheng H, Caldwell MC, Hutter D, Liu Y, Holbrook NJ, and Gorospe M (2000b). HuR regulates p21 mRNA stabilization by ultraviolet light. *Mol. Cell. Biol.* 20, 760–769. [PubMed: 10629032]
- Wang W, Yang X, Cristofalo VJ, Holbrook NJ, and Gorospe M (2001). Loss of HuR influences gene expression during replicative senescence. *Mol. Cell. Biol.* 21, 5889–5898. [PubMed: 11486028]
- Wang W, Fan J, Yang X, Fürer S, Lopez de Silanes I, von Kobbe C, Guo J, Georas SN, Foufelle F, Hardie DG, et al. (2002). AMP-activated kinase regulates cytoplasmic HuR. *Mol. Cell. Biol.* 22, 3425–3436. [PubMed: 11971974]
- Wang W, Yang X, López de Silanes I, Carling D, and Gorospe M (2003). Increased AMP-activated kinase activity during cellular senescence linked to reduced HuR function. *J. Biol. Chem.* 278, 27016–27023. [PubMed: 12730239]
- Wang W, Yang X, Kawai T, López de Silanes I, Chen P, Chook YM, Quensel C, Köhler M, and Gorospe M (2004). AMPK-regulated phosphorylation and acetylation of importin α 1: involvement in the nuclear import of RNA-Binding protein HuR. *J. Biol. Chem.* 279, 48376–48388. [PubMed: 15342649]
- Wang W, Martindale JL, Yang X, Chrest FJ, and Gorospe M (2005). Increased stability of the p16 mRNA with replicative senescence. *EMBO Rep.* 6, 158–164. [PubMed: 15678155]
- Wek RC, Jiang HY, and Anthony TG (2006). Coping with stress: eIF2 kinases and translational control. *Biochem. Soc. Trans.* 34, 7–11. [PubMed: 16246168]
- Wilczynska A, Aigueperse C, Kress M, Dautry F, and Weil D (2005). The translational regulator CPEB1 provides a link between dcp1 bodies and stress granules. *J. Cell Sci.* 118, 981–992. [PubMed: 15731006]

- Wilson GM, Lu J, Sutphen K, Sun Y, Huynh Y, and Brewer G (2003a). Regulation of A+U-rich element-directed mRNA turnover involving reversible phosphorylation of AUF1. *J. Biol. Chem.* 278, 33029–33038. [PubMed: 12819195]
- Wilson GM, Lu J, Sutphen K, Suarez Y, Sinha S, Brewer B, Villanueva-Feliciano EC, Ysla RM, Charles S, and Brewer G (2003b). Phosphorylation of p40AUF1 regulates binding to A+U-rich mRNA-destabilizing elements and protein-induced changes in ribonucleoprotein structure. *J. Biol. Chem.* 278, 33039–33048. [PubMed: 12819194]
- Wu WS (2006). The signaling mechanism of ROS in tumor progression. *Cancer Metast. Rev.* 25, 695–705.
- Xu YH and Grabowski GA (1999). Molecular cloning and characterization of a translational inhibitory protein that binds to coding sequences of human acid β -glucosidase and other mRNAs. *Mol. Genet. Metab.* 68, 441–454. [PubMed: 10607473]
- Xu YH, Busald C, and Grabowski GA (2000). Reconstitution of TCP80/NF90 translation inhibition activity in insect cells. *Mol. Genet. Metab.* 70, 106–115. [PubMed: 10873392]
- Xu N, Chen C and Shyu A-B (2001). Versatile role for hn-RNP isoforms in the differential regulation of cytoplasmic mRNA turnover. *Mol. Cell. Biol.* 21, 6960–6971. [PubMed: 11564879]
- Xu YH, Leonova T, and Grabowski GA (2003). Cell cycle-dependent intracellular distribution of two spliced isoforms of TCP/ILF3 proteins. *Mol. Genet. Metab.* 80, 426–436. [PubMed: 14654356]
- Zhang W, Wagner BJ, Ehrenman K, Schaefer AW, DeMaria CT, Crater D, DeHaven K, Long L, and Brewer G (1993). Purification, characterization, and cDNA cloning of an AU-rich element RNA-binding protein, AUF1. *Mol. Cell. Biol.* 13, 7652–7665. [PubMed: 8246982]

Figure 1. Oxidative stress-activated pathways influencing TTR-RBP activity.

Green boxes: effector kinases in signaling cascades activated or repressed by oxidative stress. Yellow ovals: TTR-RBPs that are downstream of the effector kinases, either as direct phosphorylation substrates (solid arrow) or as indirect effectors (discontinuous arrow). '?', evidence of phosphorylation available only from *in vitro* studies. Phosphorylated residues (threonines and serines) are indicated below the oval and phosphorylation linked to association with 14-3-3 (orange) is shown. Blue squares: changes in subcellular localization, association with cellular compartments (SGs, exosome) or binding to target mRNAs following modification of TTR-RBPs by the signaling cascades. Black boxes: consequences of TTR-RBP/RNP modifications upon the expression and translation of the mRNA.

Table 1

TTR-RBPs influencing the stability and translation of oxidative stress-regulated mRNAs.

ROS-regulated target mRNAs	TTR-RBPs	Posttranscriptional influence	Changes in TTR-RBP with senescence/aging
cyclin D1, c-myc, c-fos, TS, GM-CSF, TNF- α , IL-1 β , IL-3, PTH, p16, p21, GADD45a, COX-2 TNF- α , IL-3	AUF1	mRNA decay	Down (HDFs)
c-fos, c-jun, iNOS, TNF- α , and IL-2	BRF1	mRNA decay	(Unknown)
GM-CSF, c-fos, TNF- α , COX-2, IL-3	KSRP	mRNA decay	(Unknown)
COX-2, TNF- α , c-myc, CALM2,	TTP	mRNA decay	Up (mouse B cells)
SNRPF, CASP8	TIA-1	Translation decrease	(Unknown)
COX-2, TNF- α , c-myc,	TIAR	Translation decrease	(Unknown)
EIF4A1, EIF4E2, EEF1B2, PXN, EIF5A, and APAF1 c-fos, p21, cyclin A2, cyclin B1,	HuR	mRNA stabilization	Down (HDFs)
cyclin D1, iNOS, GM-CSF, VEGF, SIRT1, TNF- α , bcl-2, mcl-1, COX-2, γ -GCSH, uPA, uPAR, IL-3, MKP-1, p53, ProTa, CAT-1, cytochrome c, MKP-1		Translation increase	
p27, IGF-IR, Wnt5a, TNF- α		Translation decrease	

Listed are examples of mRNAs whose half-life and/or translational status are regulated in response to oxidative damage (column 'ROS-regulated target mRNAs'), the TTR-RBPs reported to associate with these mRNAs (column 'TTR-RBPs'), and the consequences of such RNP associations (column 'Posttranscriptional influence') upon the expression of the target mRNAs. Available information on the changes in TTR-RBP levels with increasing age and/or senescence is also indicated (column 'Changes in TTR-RBP with senescence/aging'). See the text for additional details.