Decoding ARE-mediated decay: is microRNA part of the equation?

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Messenger ribonucleic acids (mRNAs) containing adenine/uridine-rich elements (AREs) in their 3′ untranslated region are particularly labile, allowing for the regulation of expression for growth factors, oncoproteins, and cytokines. The regulators, effectors, and location of ARE-mediated decay (AMD) have been investigated by many groups in recent years, and several links have been found between AMD and microRNA-mediated decay. We highlight these similarities, along with recent advances in the field of AMD, and also mention how there is still much left unknown surrounding this specialized mode of mRNA decay.

Introduction

One mechanism used by cells to prevent the overexpression of genes is to target their mRNA for decay. Although several destabilizing elements have been described to alter mRNA stability, the most widely studied is the adenine/uridine-rich element (ARE), which often includes a repeat of the AUUUA pentamer. AREs are found in the 3′ untranslated region of certain mRNAs and have been shown to severely decrease the stability of the mRNA in which they reside. The involvement of AREs in the decay of mRNA is described as ARE-mediated decay (AMD; Barreau et al., 2005). In recent years, many advances have been made in the field of AMD relating to its effectors, regulators, and location. The physiological significance of AREs and AMD has also been revealed through several studies (Gingerich et al., 2004) that underscore the importance of tightly regulating the AMD process.

Another form of mRNA degradation that has received much attention lately involves microRNAs (miRNAs). miRNAs are derived from short hairpin RNA fragments, which are processed through a specific pathway to yield oligomers complementary to specific messages. When these oligomers then interact with their targets, one of two outcomes is observed: either translation is repressed or the target mRNA molecule is sentenced to degradation (Filipowicz et al., 2008). Interestingly, recent studies have indicated that some players in the miRNA pathway may interact with and affect the fate of ARE-containing messages (Jing et al., 2005; Vasudevan et al., 2007). In this mini-review, we will highlight what is known regarding AMD, how the rapidly evolving miRNA field may tie in, and where recent work may lead. We will also mention areas of controversy that may complicate future directions.

Regulators and effectors: a roster for AMD

Given the fact that AMD allows control over protein expression, it is not surprising that the various ARE binding proteins (AUBPs) play entirely different roles in regulating the stability of ARE mRNAs (Bevilacqua et al., 2003). Some direct ARE mRNAs toward rapid decay by AMD (e.g. tristetraprolin [TTP]; Lai et al., 1999; Lykke-Andersen and Wagner, 2005), others increase the stability of their mRNA ligands (e.g. HuR; Brennan and Steitz, 2001), and still others may do both (e.g. AUF-1/ hnRNP D; Barreau et al., 2005). A series of studies have also shown that certain AUBPs, such as TIA-1/TIAR and HuR, are capable of influencing mRNA translation (Barreau et al., 2005), and although it is not known if this activity of AUBPs is related to AMD, it certainly merits further attention.

Interestingly, most AUBPs have not yet been shown to be the direct executors of AMD but rather recruit and regulate effectors of this process (Table I, AUBPs). There exist only a limited number of known enzymes capable of degrading mRNA, and so it is not surprising that many of them have been linked to AMD (Table I, Degradation machineries; Chen et al., 2001; Gingerich et al., 2004; Parker and Sheth, 2007). The most prominent of these are the ribonucleases (RNases), of which there exist two types: exo- and endoribonucleases. The most common exoribonucleases, performing 3′ to 5′ degradation, exist in a large complex known as the exosome (Bousquet-Antonelli et al., 2000; Parker and Song, 2004). This complex, with various exonuclease subunits, also contains proteins that may be capable of binding directly to AREs. It was found that the subunits PM-Scl-75, OIP2, and RRP41 can specifically bind to AREs via their RNase PH domain (Mukherjee et al., 2002; Anderson et al., 2006).

Recent studies have demonstrated that in some cases, 5′ to 3′ mRNA decay is also significant (Stoecklin et al., 2006). The major player responsible for this nonexosomal ribonuclease

Table I. **Key players of AMD and their link to miRNA**

	Links to AMD	Links to miRNA	Major references
AUBPs			
AUF-1/ hnRNP D	Various effects on ARE mRNA stability; associates with exosome components		Chen et al. (2001); Barreau et al. (2005)
BRF1	Destabilizes ARE mRNA; associates with many degradation enzymes		Lykke-Andersen and Wagner (2005)
HuR	Stabilizes ARE mRNA	Rescues miR122 translationally repressed ARE mRNA from PBs	Brennan and Steitz (2001); Bhattacharyya et al. (2006)
KSRP	Destabilizes ARE mRNA; associates with many degradation enzymes		Chen et al. (2001); Chou et al. (2006)
TTP	Destabilizes ARE mRNA; associates with many degradation enzymes	Binds miR16 and AGO2	Lai et al. (1999); Chen et al. (2001); Fenger-Grøn et al. (2005); Jing et al. (2005); Lykke-Andersen and Wagner (2005); Hau et al. (2007)
Degradation machineries			
AGO2	Associates with TTP	miRNA processing and many other roles	Jing et al. (2005); Filipowicz et al. (2008)
CCR4	Associates with TTP and BRF1	Required for miRNA-mediated decay	Lykke-Andersen and Wagner (2005); Behm-Ansmant et al. (2006)
Decapping components	Associates with TTP and BRF1; required for AMD	Required for miRNA-mediated decay	Lykke-Andersen and Wagner (2005); Rehwinkel et al. (2005); Stoecklin et al. (2006); Behm-Ansmant et al. (2006); Lin et al. (2007)
Exosome	Certain subunits have been shown to associate with AREs directly and several subunits also bind to AUBPs; required for AMD		Chen et al. (2001); Mukherjee et al. (2002); Lykke-Andersen and Wagner (2005); Anderson et al. (2006); Lin et al. (2007)
GW182		Required for miRNA-mediated decay	Rehwinkel et al. (2005); Filipowicz et al. (2008)
PARN	Associates with KSRP and is activated by TTP; required for AMD		Lai et al. (2003); Chou et al. (2006); Lin et al. (2007)
Xrn1	Associates with TTP and BRF1; required for AMD		Lykke-Andersen and Wagner (2005); Stoecklin et al. (2006); Lin et al. (2007)

This table lists the AUBPs (for a more thorough listing of the stabilizing and destabilizing roles of AUBPs, see Barreau et al. [2005]) and degradation enzymes that have been implicated in AMD. The links that these proteins have to AMD, as well as to miRNA-based processes, are highlighted, with select references (those underlined are in relation to miRNA and those not underlined are in relation to AMD).

activity is Xrn1 (Larimer and Stevens, 1990). Intriguingly, both Xrn1 and PM-Scl-75 have been shown to be essential for adequate AMD (Yang et al., 2004a; Stoecklin et al., 2006), suggesting that more than one pathway is being used by this process (Fig. 1). Regardless of the direction exonuclease cleavage occurs in, other factors, such as decapping enzymes and deadenylases, are also typically implicated, and these have also been shown to associate with AUBPs (Table I). Evidence has also pointed toward endonucleases being involved in cleaving ARE mRNA. GAP-SH3 binding protein and the erythroid cell–enriched endoribonuclease have actually been shown to target the 3′ untranslated regions of ARE mRNA (Wang and Kiledjian, 2000; Tourriere et al., 2001; Schoenberg, 2007), making them possible suspects in AMD .

Another class of endoribonucleases that has also received much attention lately is the Argonaute (AGO) proteins. These endonucleases are clearly linked to miRNA-mediated gene silencing, and growing evidence supports that this newfound pathway of gene expression regulation is somehow related to AMD.

miRNA: the missing piece of the puzzle?

miRNAs have been shown to influence gene expression both by modulating translation and by causing the degradation of target mRNAs, although it is uncertain if the latter of these effects is a consequence of the former (Filipowicz et al., 2008). miRNAs are typically found associated with various factors, which together form microRNPs (miRNPs). A core component of miRNPs is the AGO protein, which exists in various isoforms, some of which are capable of interfering with translation and of degrading mRNA by way of their endonuclease activity (Filipowicz et al., 2008; Wu and Belasco, 2008). It is intriguing to note that these two effects of miRNA mirror those linked to AUBPs, suggesting that perhaps the AMD and translational roles of AUBPs are mediated, or at least influenced, by miRNA.

AMD and miRNA-mediated decay involve some of the same players, such as the CCR4 deadenylase complex and the decapping enzymes Dcp1/2 (Behm-Ansmant et al., 2006). Beyond this, a few important studies have actually shown interactions between the two processes. Jing et al. (2005) found that Dicer, a key player in the biogenesis of miRNAs, is a required component for the degradation via AMD of the ARE-containing message TNFα. They reported that miR16 targets a sequence located outside the 34-nt ARE region (Vasudevan and Steitz, 2007) that is needed for AMD of TNFα mRNA and that this miRNA indirectly associates with TTP through the AGO complex. The authors speculated that ARE recognition by TTP aids miR16 in binding to a target sequence and that the miR16-associated
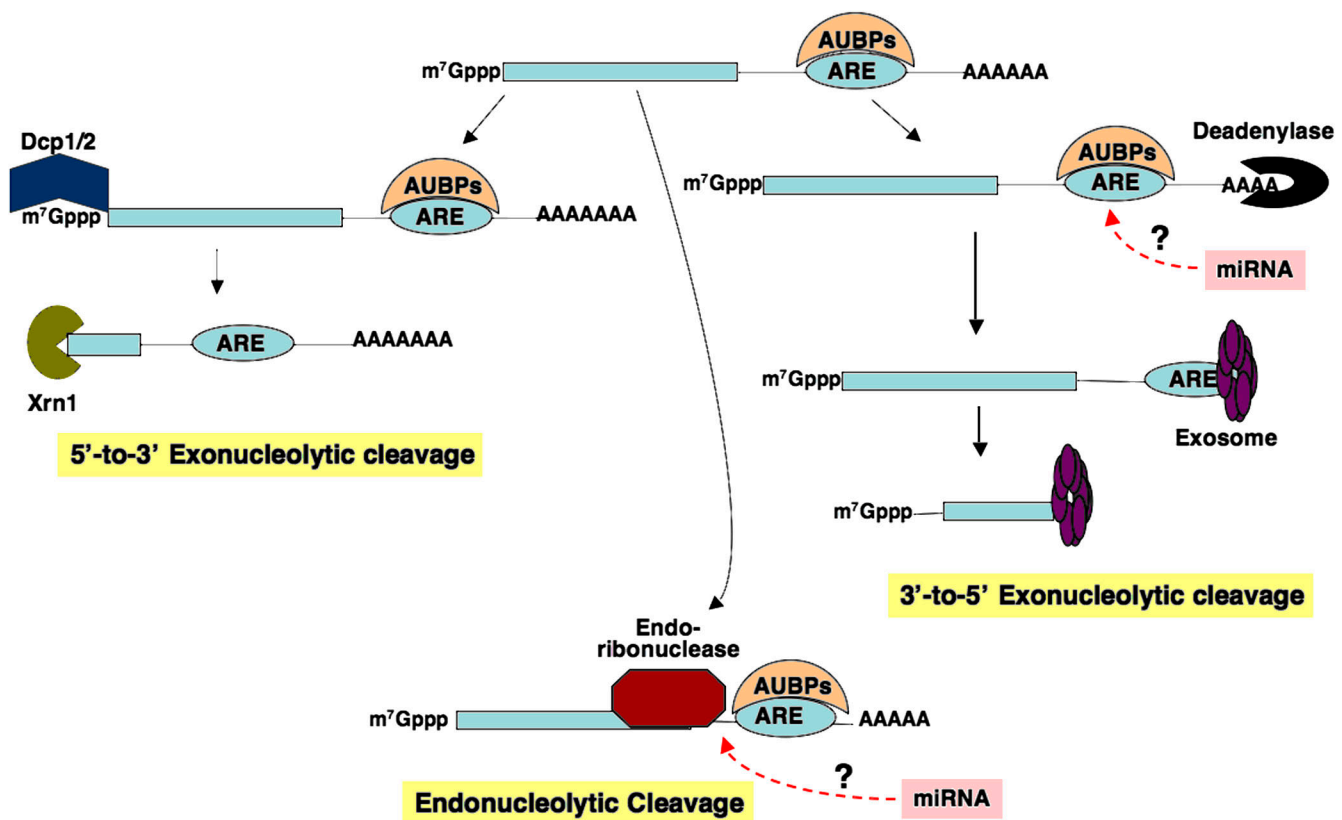
Figure 1. **Model for AMD.** Based on current literature, we propose three major pathways by which AMD is executed. In the first, AUBPs promoting degradation (e.g. TTP) may bind the ARE of the target mRNA and help recruit decapping enzymes such as Dcp1/2. After decapping, the 5′ to 3′ exoribonuclease Xrn1 may then carry out 5′ to 3′ decay. In the second, AUBPs may recruit endoribonucleases to internally cleave the target mRNA. Some data implicate miRNAs in this AUBP interaction, such as the miR16–AGO2–TTP complex (Jing et al., 2005). In the third, AUBPs may recruit deadenylases (such as PARN or CCR4) to remove the poly (A) tail from the 3′ terminus of the mRNA, and 3′ to 5′ degradation may then occur by way of the exosome. miRNP complexes may also be involved in recruiting the machineries for this pathway. Stabilizing AUBPs, such as HuR, may be implicated in one or more of these pathways by competing with binding of destabilizing AUBPs or by preventing miRNA–mRNA interactions.

complex components, such as AGO2, can then mediate the AMD effect. Could this be an example of a collaborative effort between a miRNA and an AUBP, permitting a more stable interaction with the target mRNA, which then allows the recruitment of the degradation machinery? Although most miRNA-mediated regulation requires perfect complementarity in the "seed" sequence of the miRNA (bases 2–8; Filipowicz et al., 2008), the complementarity between miR16 and its target mRNA does not exist in this region. Perhaps the collaboration between miR16 and TTP is a means of regulating the effects of miR16.

If a known destabilizing AUBP, such as TTP, can assist the miRNA-mediated degradation of a target message, then it would be reasonable to speculate that a stabilizing AUBP, such as HuR, could interfere with miRNA binding. The idea of HuR interfering with the effects of miRNA is not unheard of. A recent study by Bhattacharyya et al. (2006) found that HuR was capable of rescuing translationally repressed mRNA, most likely by interfering with the association of miR122 with ARE mRNA. If TTP can assist a miRNA in carrying out decay, then having AUBPs either interfere with or support the translational effect of miRNA is just as likely. This supports the idea that RNA binding proteins and miRNAs may regulate each other's effects by competing for binding or complementing the binding of one another (George and Tenenbaum, 2006).

Recent results from Vasudevan and Steitz (2007) further support this idea. They showed that a well-known AUBP, fragile X mental retardation–related protein 1 (FXR1), binds to the ARE of TNFα mRNA to promote translation during serum starvation in an AGO2-dependent manner (Vasudevan and Steitz, 2007). For translation of the ARE mRNA to increase, both FXR1 and AGO2 had to be present, showing that it is both the cellular environment and an interplay between AUBPs and miRNA factors that influence gene expression. A subsequent study demonstrated that this translational up-regulation depended on miR369-3 to bring FXR1 and AGO2 to the ARE and that miRNAs enable the transition between the repression and promotion of translation (Vasudevan et al., 2007). Collectively, these studies show that translation may be influenced by players associated with both AMD and miRNAs and that only through cooperation can the desired outcome be obtained.

AMD and miRNA do more than share effectors of degradation. Their players have been shown to operate codependently, and the studies showing these relationships suggest that they work together in a variety of situations. Another commonality between these two involves *where* in the cell they carry out their roles, and, not surprisingly, uncertainty surrounds these details of AMD as well.

Common grounds

As mentioned earlier, the decapping enzyme complex has been linked to both AMD and miRNA function. It was noticed that these enzymes, along with several other factors that promote decapping, localized to cytoplasmic foci, and these have since been named processing bodies (PBs; Eulalio et al., 2007; Parker and Sheth, 2007). In addition, several mRNA degradation enzymes have been found to aggregate in another species of cytoplasmic granule, which specifically form under stressful conditions, named stress granules (SGs; Anderson and Kedersha, 2006). Both of these cytoplasmic bodies have raised interest because of their link to AMD and to miRNA-mediated effects, with the potential of being the specific loci where these processes are modulated.

PBs: into the lion's den. The interaction between certain AUBPs and PB-associated proteins raised the possibility of a direct link between AMD and PBs. The most relevant of these binding proteins is TTP. TTP has been shown to interact with Dcp2 and other components of the decapping complex (Fenger-Grøn et al., 2005). TTP, as well as several AUBPs, has also been shown to associate with various other PB-associated factors, including Xrn1, CCR4 (Lykke-Andersen and Wagner, 2005; Hau et al., 2007), and the exosome (Chen et al., 2001), particularly the PM-Scl-75 subunit (Hau et al., 2007). These observations suggest that TTP and other AUBPs help recruit degradation factors to ARE mRNAs. This, and the result that exosome components can directly bind AREs (Mukherjee et al., 2002; Anderson and Kedersha, 2006), support the hypothesis of van Hoof and Parker (2002) that the exosome and, perhaps, other components of the degradation machinery are recruited both by AUBPs bound to the target mRNA and by the RNAs themselves.

Several knockdown studies have been done to assess the influence of different factors on the existence of PBs and on AMD. For example, knockdown of Xrn1 or Dcp2 caused an accumulation of ARE mRNAs in PBs and a decrease in degradation (Franks and Lykke-Andersen, 2007), whereas the downregulation of various components of 5′ to 3′ and 3′ to 5′ exonuclease systems also diminished the amount of AMD (Lin et al., 2007). Nevertheless, the results of these studies are not always complementary. Perhaps the most relevant example is that of knocking down GW182. GW182 is documented to be required for both PB formation (Yang et al., 2004b) and miRNA activity (Rehwinkel et al., 2005). When the expression of GW182 is reduced, however, there is no observable effect on AMD, even when a significant decrease in the number of visibly detectable PBs is seen (Stoecklin and Anderson, 2007). This highlights the fact that despite the ability of some AUBPs to interact with PB-associated decay enzymes, there is not adequate information to confirm a functional link between AMD and the recruitment of ARE mRNAs by PBs. There is also a mounting discussion over the role PBs play in repressing translation (Coller and Parker, 2005; Parker and Sheth, 2007), which is significant for both miRNA effects and the roles of AUBPs. Equally intriguing are observations showing that PBs can interact with SGs and that this interaction may be responsible for deciding the AMD fate of target mRNA (Kedersha et al., 2005).

SGs: live or let die. SGs were originally observed as localization centers for specific mRNAs in cells exposed to heat shock (Nover et al., 1989). In mammalian cells, various environmental stressors can induce the formation of SGs (Anderson and Kedersha, 2006). SGs are believed to stabilize and block the translation of certain mRNAs (Kedersha et al., 2005; Mazroui et al., 2007) and then, when the stress is relieved, SGs may direct these mRNAs either back to the polysome or to machineries responsible for their degradation (Anderson and Kedersha, 2006; Kedersha and Anderson, 2007). Several RNA binding proteins that have been shown to be essential for SG formation localize to SGs such as TIA-1/TIAR (Kedersha and Anderson, 2002). HuR, TTP, and GAP-SH3 binding protein, among other AUBPs, also accumulate in these foci (Gallouzi et al., 2000; Tourriere et al., 2003; Stoecklin et al., 2004).

Although several PB components, such as Dcp1/2 and GW182, are not present in SGs, others, such as Xrn1, are (Anderson and Kedersha, 2006). Additionally, overexpressing TTP and BRF1 has been shown to cause stable interaction between PBs and SGs. These intriguing links between two cytoplasmic granules encourage speculation regarding their relationship. Is it possible that under stressful conditions, AUBP-bound mRNAs first localize to SGs and are then directed to PBs for decay? The PB–SG relationship has been further complicated after observations that the formation of PBs and SGs are independent (Kedersha et al., 2005). Moreover, some stresses that induce SG formation actually prevent both PB development and the decay of mRNA (Mazroui et al., 2007). These results make it difficult to develop an unambiguous model regarding the cellular location of AMD. Similar localization issues are also a problem in developing a unified model for miRNA-mediated repression (Filipowicz et al., 2008). When HuR rescues miRNA-repressed mRNA, it does so by causing the mRNA to leave PBs (Bhattacharyya et al., 2006). It was also reported that in the presence of miRNAs, AGO proteins are capable of dynamically associating with SGs, where these enzymes play a role in translation silencing but not in message decay (Leung et al., 2006). Although the compositions and proposed functions of PBs and SGs may differ, there is much evidence that they are both involved in both AMD and in miRNA-mediated repression.

Unsolved mysteries

As advances in the field of mRNA decay are made, it is apparent that AUBPs are a crucial component of AMD and that modification of AUBPs may regulate ARE mRNA decay (Stoecklin et al., 2004). At the same time, the localization of AMD-linked players is of great importance, and another potential complication in constructing a model for AMD is the possibility that the granules discussed are more complex than they appear. With the observations that the formation of SGs can be initiated in an eIF2α phosphorylation-dependent and -independent manner, it was proposed that different types of SGs may exist (Anderson and Kedersha, 2006; Mazroui et al., 2006). If true, then it is reasonable to hypothesize that different SGs can direct messages differently. This theory actually supports the various ways that SGs and PBs have been shown to interact. If there are various classes of SGs, then it would be reasonable to suspect that some support PB formation and AMD, whereas others promote

alternative functions. What are taken to be a type of SG at this time could ultimately be shown to exist primarily for the purpose of reinitiating translation of mRNAs. Ultimately, SGs may be implicated in the balance a cell mediates between survival and death after stress, and differing granule classes and interactions may transiently exist as the cell gauges its fate (Mazroui et al., 2007). Similarly, although PBs and GW bodies were considered to be the same entity after their discovery, this conclusion may have been premature, as they may ultimately be distinct subsets of cytoplasmic bodies. It has been observed that GW bodies disappear with cell cycle arrest (Eulalio et al., 2007), whereas PBs remain (Vasudevan and Steitz, 2007). Moreover, AMD-linked players, such as the FXR1 and AGO2 members of the miRNA pathway, were originally thought to be components of PBs but have been shown to colocalize to GW bodies rather than Dcp1-containing cytoplasmic foci (Vasudevan and Steitz, 2007). This may explain why PBs could be seen in yeast even though they do not have an analogue of GW182 (Ding and Han, 2007). Even the recently proposed exosome granules, which may serve as a major site for AMD, could be distinct from PBs (Lin et al., 2007). Another important consideration is whether ARE mRNAs are brought to these preexisting cytoplasmic granules or whether a concentration of AMD-targeted mRNA, bound to its various factors, is necessary for the formation of SGs or PBs.

These discrepancies invite further investigation into the localization of AMD. Meanwhile, the relationship between AMD and miRNA-mediated decay warrants attention. Not only are there similar aspects to the processes but the colocalization of certain players strongly supports an underlying coordination. Ultimately, the details surrounding AMD, that is, the players involved in mediating such decay, the mechanism, the timing, the localization, and its regulation, leave much mystery regarding this process. Investigation into AMD has so far demonstrated quite well the validity of the adage that the more one knows, the more one learns is left unknown. For a process linked to so many evolving fields, there is little doubt that the existing facts about AMD may drastically evolve, all the while bringing us closer to appreciating exactly how such tight regulation of cell function can be dictated by a series of adenine/uridine repeats.

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