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Untranslated regions (UTRs) orchestrate translation reprogramming in cellular stress responses

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ABSTRACT

Stress is the result of an organism's interaction with environmental challenges. Regulations of gene expression including translation modulations are critical for adaptation and survival under stress. Untranslated regions (UTRs) of the transcripts play significant roles in translation regulation and continue to raise many intriguing questions in our understanding of cellular stress physiology. IRES (Internal ribosome entry site) and uORF (upstream open reading frame) mediated alternative translation initiations are emerging as unique mechanisms. Recent studies have revealed novel means of mRNAs stabilization in stress granules and their reversible modifications. Differential regulation of select transcripts is possible by the interplay between the adenine/uridine-rich elements (AREs) in 3'UTR with their binding proteins (AUBP) and by microRNA-mediated effects. Coordination of these various mechanisms control translation and thereby enables appropriate responses to environmental stress. In this review, we focus on the role of sequence signatures both at 5' and 3'UTRs in translation reprogramming during cellular stress responses.

1. Introduction

In their constant interaction with the surrounding environment, organisms encounter a number of stressors such as temperature shock, exposure to toxins, oxidative stress and nutrient deprivation. The ability to adapt and survive in these conditions is a fundamental requirement of all organisms. Based on the nature and intensity of stressors, cells mount different survival or adaptive repair mechanisms such as heat shock response, DNA damage response, oxidative stress response and unfolded protein response. At the cellular level, stress responses essentially involve complex regulations of gene expressions which are of interest to both basic biology and molecular medicine (Kültz, 2005).

Proteins are the workhorses of cells and catalyze most of the cellular processes including repair mechanisms; understandably, their levels are tightly regulated during cellular stress responses. Protein synthesis can be modulated at successive steps of gene expression, from chromatin modulation to translation. Translation is the final step in the flow of genetic information and contributes considerably to protein pool variations. Compared to the *de novo* synthesis of mRNA, their processing and transport to the cytoplasm; regulation at the level of translation using pre-existing mRNA allows for rapid changes in the protein pool. This kind of regulation is critical, especially when cells are exposed to stressors which require immediate alterations in the cellular physiology (Holcik and Sonenberg, 2005; Liu and Qian, 2014).

The stress-induced translation reprogramming involves two broad categories of regulations: first, global repression of translation to avoid the synthesis of most of the proteins; and second, selective translation of proteins which are essential for the cellular stress responses. Global translation inhibition is mediated by interference in cap recognition by eIF4E and or eIF2 ternary complex formation. Briefly, under normal conditions, classical cap-dependent translation initiation includes recognition of 5'cap (m7Gppp) by eIF4E along with eIF4G and eIF4A. The formation of the ternary complex (eIF2α-Met-tRNAi–GTP) is the next step for assembly of ribosome subunits for scanning of the start codon to initiate protein synthesis. Under stress conditions, several signaling pathways mediate inhibition of translation (Sengupta et al., 2010).

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Mammalian target of rapamycin complex 1 (mTORC1) is one of the major stress response signaling mechanism. Nutrient (amino acid) stresses influence the mTORc1 pathway which in turn prevents the cap recognition step of translation (Sengupta et al., 2010). Four classes of eIF2α kinases such as general control non-derepressible-2 (GCN2), protein kinase double-stranded RNA-dependent (PKR), PKR-like ER kinase (PERK) and heme-regulated inhibitor (HRI) are activated by different kinds of stressors (nutrient stress, virus infection, ER stress). Subsequent phosphorylation of eIF2 prevents the formation of the ternary complex, leading to global translation inhibition (Donnelly et al., 2013).

The selective translation of proteins during stress conditions mainly involves sequence signatures present within the untranslated regions (UTR). There are unique features in both 5' and 3' UTRs of stress gene transcripts, which possibly play critical roles in the preferential regulation of protein synthesis (Fig. 1). Internal ribosome entry site (IRES), upstream open reading frame (uORF), terminal oligopyrimidine tract (TOP) and potential secondary structures represent functional elements present within the 5'UTR. Similarly, 3'UTR motifs such as AU-rich elements (ARE) and microRNAs binding elements (MRE) determine transcript abundance. Functions of UTRs in translation under normal physiological conditions are well described in the literature (Barrett et al., 2012). However, the comprehensive role of these unique functional motifs is significant in the context of cellular stress conditions. In this review, we focus on the contribution of these RNA motifs along with the related novel translation mechanisms in cellular stress responses.

2. Untranslated regions (5'UTRs)

2.1. IRES function in preferential translation of stress genes

When cells are exposed to different types of stressors, classical protein synthesis pathways are inhibited, while alternative mechanisms rescue translation of select proteins that have essential roles in protecting the cells under difficult circumstances. Among mechanisms of preferential protein synthesis, IRES-mediated initiation is considered significant. IRESes are specialized cis-acting elements in the 5'UTR that allow direct recruitment of eukaryotic 40 S ribosomes

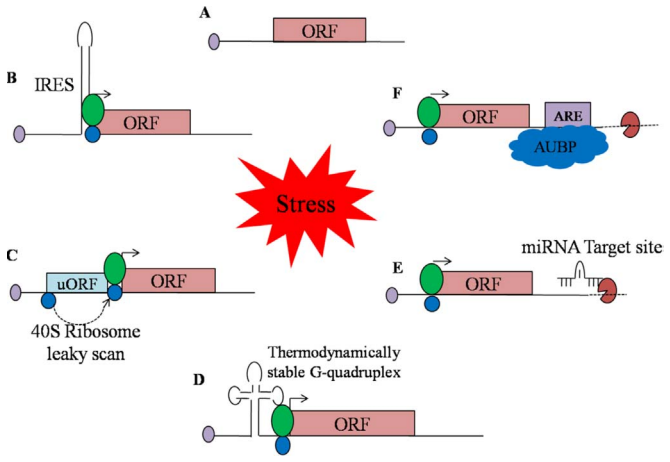

Fig. 1. Functions of regulatory RNA motifs of UTRs in cellular stress responses. During stress, translation initiation of house-keeping proteins is inhibited (A); whereas selective translation initiation of certain transcripts is mediated by different RNA motifs present in the 5'UTR. These include internal ribosome entry site (IRES) with cap-independent translation initiation (B), upstream open reading frame (uORF) through leaky 40 S ribosome scan mechanisms (C) and regulation by thermodynamically stable structures called G-quadruplexes (D). Cellular stress responses induces differential turnover of transcripts by sequence motifs present in the 3'UTR. These mechanisms include miRNA response elements (MRE) (E) and AU rich elements (ARE) along with their binding proteins (AUBP) (F).

without the need of cap-recognition by eIF4E (Jackson, 2013). Though initially identified in viral transcripts, cellular mRNAs were later found to have IRESes. In contrast to their viral counterparts, cellular IRESes lack any consensus sequence motifs making their *in-silico* identification very difficult (Thompson, 2012). However, cellular IRESes have longer 5'UTR that are rich in GC elements and show a higher predominance of acquiring secondary structures. These characters considerably reduce the classical cap-dependent mechanism of scanning the start codon by the pre-initiation complex. Still, there is no clarity in defining IRES as a mechanism distinct from cap-dependent initiation. Different experimental strategies have been suggested to confirm the identity of IRES-mediated translations (Komar and Hatzoglou, 2011).

One of the significant factors is the conditions that favor IRES-mediated translation initiation. It has been found that many pathophysiological and stress conditions cause a substantial increase in cellular IRESes-mediated translations (Thakor and Holcik, 2011). Such conditions include, but are not limited to, endoplasmic reticulum (ER) stress, hypoxia, thermal shock and nutrient limitation. Cells are programmed to maintain the well-being of the organism as a whole. Hence, depending on the intensity of damage, cells mount elaborate stress responses that may have survival effects or induce cell death (apoptosis). It is striking that many of the cellular mRNA that contain IRES encode proteins which are involved in these crucial decision-making pathways. The subsets of survival proteins and cell death inducing (pro-apoptotic) proteins have been found to be translated under the influence of IRES in their transcripts (Table 1). Heat shock proteins (HSPs), a family of cell protective chaperones are preferentially synthesized during stress conditions using IRES mechanisms (Dinkova et al., 2005; Rocchi et al., 2013). Similarly, cell death inducing pro-apoptotic proteins such as Apaf-1, p57 (Kip2) and GADD153 were synthesized by IRES-mediated mechanisms (Ungureanu et al., 2006; Young et al., 2008; Nishitoh, 2011). Therefore, based on the severity and duration of stress involved, IRESes may play a role in cell-fate decisions either activating survival proteins to allow the repair of cellular damage or synthesis of pro-apoptotic proteins to induce cell death.

2.2. Secondary structure of 5'UTR to sense the temperature stress: Eukaryotic RNA thermometer?

Unlike eukaryotes, prokaryotic translation begins with the direct binding of the ribosomes to the initiation codon in the optimum sequence context (Shine-Dalgarno sequence and ribosome binding site-RBS). The sequence and structural features of mRNA in this region influence the translation efficiency (Shah and Gilchrist, 2010). In some bacteria, mRNA conformations respond to changes in external environmental factors such as temperature to regulate translation efficiency. These secondary structures are dubbed as 'RNA-thermometers'. There is a possibility of similar parallel mechanisms, albeit in varied form in eukaryotes as an evolutionary remnant. In earlier studies on mammalian cells, very stable structures (delta G≥−50 kcal/mol) introduced within the 5'leader completely blocked ribosome scanning, whereas moderate structures (delta G ≤−30 kcal/mol) repressed translation by inhibiting binding of the pre-initiation complex to the mRNA (Ringnér and Krogh, 2005).

The guanine (G)-rich regions in the 5'UTRs are known to form four-stranded structural conformations called G-quadruplexes. These are the thermodynamically stable structures that are found to regulate the translation of mRNA. The formation of a G-quadruplex may be regulated by the adjacent sequences in the 5'UTRs, RNA-binding proteins or other more complex mechanisms (Bugaut and Balasubramanian, 2012). Despite their general inhibitory effect on translation, some of the G-quadruplex motifs were found to be essential for IRES-mediated cap-independent translation initiation (Morris et al., 2010). Since cap-independent mechanisms are more

Table 1
Gene transcripts with experimentally confirmed IRES mediated translation initiation during cellular stress responses.

Gene name	Functions in cellular stress response	Species	Reference
HSPA1A	Refolding misfolded proteins and/or preventing aggregation of proteins in stressed cells.	*H. sapiens*	Rocchi et al. (2013)
HSP101	Prevents aggregation of proteins in stressed cells.	*Zea mays*	Dinkova et al. (2005)
APAF1	Involved in UV stress induced apoptosis of cells	*M. musculas*	Ungureanu et al. (2006)
VEGF-A	Involved in hypoxia, physical and chemical stressors to promote proliferation of endothelium.	*M. musculas*	Young et al. (2008)
GADD153	Induced during DNA damage response	*H. sapiens*	Nishitoh (2011)
BAG1	Interacts with cellular stress response protein, GADD34 and interfere with its functions.	*H. sapiens*	Coldwell et al. (2001)
HSPA5	A molecular chaperone involved ER stress response or unfolded protein response.	*H. sapiens*	Thoma et al. (2004)
MYC	Multi-functional transcription factor enhanced in genotoxic stress	*H. sapiens*	Thoma et al. (2004)
BIRC2	Plays a cytoprotective role by preventing activation of apoptotic pathway.	*H. sapiens*	van Eden (2004)
HSP90AA1	Function in protein folding and prevent misfolding or aggregation of proteins in stressed cells.	*D. melanogaster*	Ahmed and Duncan (2004)
HIF1A	Activates several downstream genes in response to oxidative stress.	*M. musculas*	Bert (2006)
RBM3	RNA chaperone that modulates translation of other proteins in hypothermic stress.	*M. musculus*	Baranick et al. (2008)
TP53	Activated during DNA damage, Oxidative/osmatic stress and plays a role in genomic stability.	*H. sapiens*	Grover et al. (2009)
NRF2	A transcription factor mediates expression of detoxification and anti-oxidant genes.	*H. sapiens*	Shay et al. (2012)
CSDE1	Induced in cold stress and also involved in salt and drought stress tolerance in animals and plants.	*H. sapiens*	Kim et al. (2013)
WUS	Transcription factor that maintains the stem cell homeostasis in response to environmental stress.	*A. thaliana*	Cui et al. (2015)
DDB2	Tumor-inhibiting factor involved in the DNA damage response pathway	*H. sapiens*	Dai et al. (2015)
DKN2A/ p16INK4a	Tumor suppressor protein induced under hypoxic stress and controls cell cycle progression.	*H. sapiens*	Bisio et al. (2014)

prevalent during cellular stress responses; G-quadruplexes may play a role in stress-induced translation reprogramming. It was found that some of the transcripts preferentially translated under heat stress contain a putative G2 quadruplex in their 5′UTR (Lukoszek et al., 2016). These results suggested that quadruplex structures activate translation of downstream ORFs, however the mechanisms needs to be studied.

There is no direct evidence of temperature stress-sensitive UTRs structural elements in the eukaryotes as compared to the prokaryotes. Putative RNA thermometers have been identified by probing RNA structures at different temperatures in *S. Cerevisiae* (Wan et al., 2012). This study revealed a significant positive correlation between the propensity of bases upstream from the start codon to melt (thermosensitive) and the translation efficiency of the gene. The transcript-profiling data also indicated that the putative RNA-thermometers play a role in direct mRNA decay during stress. The exosome preferentially degrades unpaired RNA and is considered as the 'reader' of the RNA thermometer (Wan et al., 2012). These results indicated that most structurally stable mRNAs barely decline during heat shock, whereas mRNAs with low melting temperatures display considerable decreases in transcript levels. Despite well-studied RNA thermometers in prokaryotes, there is no clear consensus about the existence of such elements in eukaryotes. However, genome-wide profiling of RNA structures in *Arabidopsis thaliana* revealed a strong association between three-nucleotide periodic repeat patterns in the structure of coding regions and a less-structured region immediately upstream of the start codon, and higher translation efficiency (Ding et al., 2013). It may be that instead of simple RNA folding energy-based regulation, several associated mechanisms including binding of still unknown regulatory proteins may be involved in stress-induced translation regulations in eukaryotes.

2.3. uORFs action in integrated cell stress responses

uORFs are the transcript sequences in 5'UTR, defined by an initiation codon in the frame with a termination codon located upstream of the principal ORF. In the normal conditions, their presence creates a stumbling block for classical cap-dependent initiation at the main AUG and consequently decreases translation efficiency. However, in response to stress, uORFs promote synthesis of proteins from the principal ORF of the mRNA (Andreev et al., 2015). The Recent bioinformatic analysis identified that nearly 49% of the mammalian transcriptome possesses one or more uORFs (Wethmar, 2014). Conspicuously they are more common in certain classes of transcripts; particularly those involved in cellular processes such as differentiation and integrated stress responses. The uORFs mechanisms have been observed in preferential synthesis of stress-inducible regulatory proteins such as growth arrest and DNA-damage-inducible protein 34 (GADD34), DNA damage inducible transcript 3 (DDIT3) and ATF5 (Lee et al., 2009; Hatano et al., 2013; Young et al., 2015). Ribosome profiling of cultured human cells under chemical stress indicated many regulatory genes escaping global translation inhibition. The fact that nearly all of these transcripts had at least one uORF in their 5'UTR suggested a critical function of uORFs in selective synthesis of proteins as a part of the cellular stress responses (Andreev et al., 2015).

The mechanistic details of uORF functions have emerged during recent investigations. Re-initiation at the principal ORF, the combined effect of uORF and IRES and the function of the uORF-encoded regulatory peptide are the mechanisms suggested in translation reprogramming during cellular stress responses (Fig. 2). GADD34 is

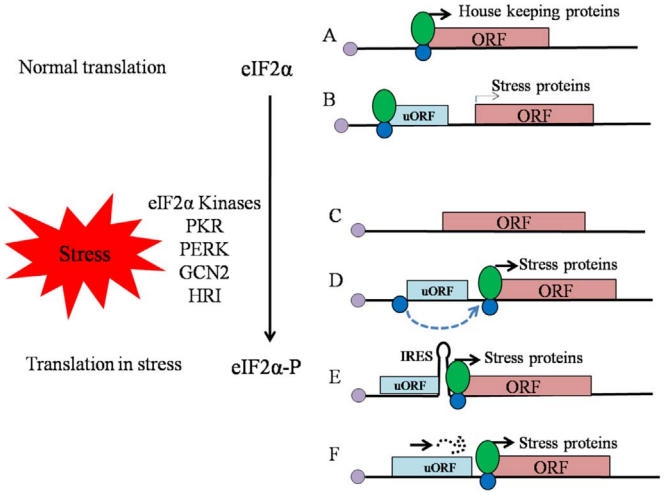

Fig. 2. uORF mechanisms in translation reprogramming during cellular stress responses. Under normal conditions, eIF2α forms ternary complex (eIF2-TC) which leads to classical cap-dependent initiation in transcripts without uORFs (A) whereas the presence of uORFs in stress protein transcripts reduces translation from principal ORF (B). Under stress conditions, the activated eIF2α kinases blocks classical cap-dependent mechanism in transcripts without uORF (C). However, the presence of uORFs facilitates translation from principal ORFs using different mechanisms. Re-initiation, in which reduced concentration of eIF2-TC during stress gives time for 40 S ribosome scanning to bypass the uORF and reinitiate at principal ORF (D). Interactions that involve both uORF and IRES elements within the 5'UTR of the stress transcripts can cause translation from principal ORF (E). The uORF encoded peptide product can have regulatory functions affecting the translation of principal ORF (F).

a member of the group of proteins whose levels are increased in stressful conditions. The GADD34 transcript has uORF that inhibits its translation under normal conditions but during stress responses, ribosomes bypass uORF and reinitiates at the principal ORF to synthesize GADD34 (Lee et al., 2009). Aminoacyl-tRNA synthetases (aaRSs) are a group of enzymes that charge amino acids on respective tRNAs and play a pivotal role in translation. One such enzyme, Glycyl-tRNA synthetases (GARS) has different gene isoforms which are differentially regulated. An intricate regulatory mechanism of both uORF and IRES results in selective translation of GARS isoforms during nutrient stress (Alexandrova et al., 2015). In another distinct mechanism, uORF-encoded peptides act as regulatory trans-factors and facilitate the translation from principal ORFs (Ebina et al., 2015). Recently, it has been found that uORF-encoded products may generate MHC I peptides which function in adaptive immunity as extracellular signatures (Starck et al., 2016). These examples show that uORFs not only provide cap-independent translation but their own products may also play a significant role in cellular responses to environmental cues.

2.4. Terminal oligopyrimidine tracts (TOP)

TOP is a 4-15-nucleotide CU-rich sequence motif at the 5' end of the transcripts which codes for components of the translational apparatus, such as ribosomal proteins and elongation factors. During nutrient stress, the translation of TOP-containing mRNAs is inhibited to prevent the energetically demanding process of ribosome biogenesis (Labban and Sossin, 2011). The selective translation repression is specifically due to the TOP motif and its associated mechanisms. It has been found that starvation-mediated activation of GCN2 (general control non-derepressible 2) and inactivation S6K (S6 Kinase) of the mTOR signaling pathway are responsible for selective repression of TOP-containing transcripts (Labban and Sossin, 2011). The stress granule (SG) associated proteins such as TIA-1 and TIAR are considered to be key factors in human TOP mRNA regulation (Damgaard anfd Lykke-Andersen, 2011). TOP mRNAs encoding poly (A) binding protein (PABP1), eEF1Aand ribosomal protein S6 (RPS6) are translated preferentially during recovery of HeLa cells from heat shock (Datu and Bag, 2013). Among other proteins, the La autoantigen is considered to be one of the trans-acting factors which bind to the TOP motif. La can interact with TOP and is implicated in the regulation of TOP mRNA translation. Recently it was found that LARP1 (La-related protein 1) acts as an important repressor of TOP mRNA translation downstream of mTORC1 by competing with eIF4G (Fonseca et al., 2015).

3. Untranslated regions (3'UTRs)

3.1. AU-rich elements (ARE)

Among other events, mRNA turnover is a critical component of translation regulation. Cell stress responses not only block classical translation initiation but also promote accumulation of untranslated or ribosome-stalled mRNAs in special structures called stress granules (SG) (von Roretz et al., 2010). SG provides temporary storage of transcripts and plays an important role in the mRNA turnover. From the SG, transcripts may be taken for translation re-initiation or considered for degradation by different mechanisms. As a consequence of stress induced translation inhibition, accumulation of mRNA and its decay machinery lead to formation discrete structures called processing bodies (P-bodies) (Eulalio et al., 2007b). However, it is unclear how SG and PB interact to determine the stabilization and or decay of target transcripts. AREs present within 3' UTRs are among the best characterized cis-acting elements determining the fate of mRNAs (von Roretz et al., 2010). Although there is no strict consensus sequence, the key motif AUUUA in multiple copies, especially in AU-rich regions, are considered as AREs. Transcripts with ARE mostly encode proteins that are involved in the regulation of the organism's response to external environmental factors. ARE-containing mRNAs are normally labile to degradation. However, in response to cellular stress, they are differentially regulated through interaction with a diverse collection of cellular trans-acting factors known as ARE-binding proteins (AUBP) (Cairrao et al., 2009). AUBP either promote mRNA decay or have stabilizing effects by locating them to PB or SG (Fig. 3).

The interactions between ARE and AUBP play important roles in trafficking and turnover of mRNAs. For example, HuR stabilizes ARE-containing mRNA such as VEGF, IκB-α and c-fos in SG during short-duration stress, later allowing their translation re-initiation (Liu, 2013; Degese et al., 2015). How exactly HuR enables differential turnover of transcripts in cellular stress responses is not yet clear. Different mechanisms have been suggested to the function of HuR, such as preventing poly A tail removal from the target mRNA, competing with other proteins or with miRNA which cause transcript decay (von Roretz and Gallouzi, 2008). Post-translation modifications of HuR such as phosphorylation, methylation and its cleavage under stress affect its association with mRNA and consequently its ability to stabilize the mRNA (Yoon et al., 2013). Further clarifying the role of these post-translation modifications will help to understand how HuR alters mRNA turnover in stress responses.

AU-rich element RNA-binding protein (AUF1), also known as heterogeneous nuclear ribonucleoprotein D (HNRNPD), is an extensively studied AUBP. AUF1 was found to promote both stabilizing and destabilizing effects on target mRNAs indicating the involvement of other associated regulatory proteins (Vázquez, Chantada et al., 2010). AUF1 recruit proteins such as the translation initiation factor eIF4G, chaperones (Hsp27 and Hsp70), heat-shock cognate protein (Hsc70), lactate dehydrogenase, poly (A)-binding protein and other unidentified proteins (White et al., 2013). These associated proteins are induced by different signaling pathways to influence ARE-mRNAs turnover. The range of associated proteins for AUF1 indicates its role in functionally related pathways which needs to be understood. Apart from well-known HuR and AUF1, it was found that Hsp70 can act as AUBP, with high binding specificity for U-rich mRNA sequences. Hsp70 stabilizes ARE-containing transcripts encoding VEGF and cyclooxygenase-2 (Cox-2) (Kishor et al., 2012). It may be concluded that ARE-containing mRNAs may contribute to the cytoprotective effects of Hsp70.

3.2. microRNA response elements (MRE)

microRNA (miRNAs) are a class of endogenous, small (~22 nucleotides) non-coding RNAs that play important roles in translation inhibition and regulation of mRNA turnover. MRE (miRNA response

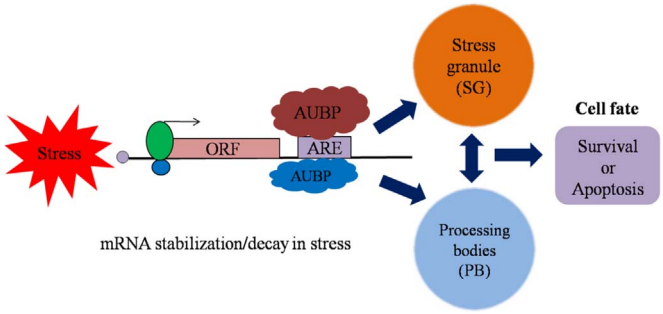

Fig. 3. Role of ARE and AUBPs in cellular stress responses. The half life of mRNA with ARE motifs in their 3'UTR is regulated by AUBP. Under stress conditions, the stabilization or degradation of ARE-mRNA that are in different stages of translation determined by their accumulation in stress granules (SG) or Processing bodies (PB). Different results including re-engagement of polysomes on previously protected transcripts or their degradation are expected by the interactions and sharing of transcripts between PB and SG. Stress induced stabilization or decay of transcripts encoding survival/apoptotic proteins determine the cell fate.

elements) are sequences in the 3'UTRs of transcripts and typically have a conserved stretch of 7 nucleotides that are able to base pair with the corresponding miRNA sequence (Nahvi et al., 2009). Gene expression networks regulated by miRNA were found to coordinate cellular stress responses (Schober et al., 2015). Experimental evidence suggests that several miRNA significantly regulate the synthesis of proteins involved in the stress response pathway. For example, HSPA5/GRP78 is a molecular chaperone that promotes cell survival under certain stress conditions. During a stroke, miR-181 levels increase in ischemic tissues, potentiating the injury by targeting and depleting the levels of HSPA5/GRP78 (Ouyang et al., 2012). Similarly, miRNA-mediated improper regulation of stress-responsive proteins was found to predispose to several disease outcomes (Emde and Hornstein, 2014). Single miRNA may target multiple genes (pleiotropic effect) and hence may facilitate integrated stress response mechanisms (Jia et al., 2014). Recently, high-throughput methods have provided a fillip to the study of miRNA expression profiling under stress conditions in higher animals and plants. *PASmiR*, a database of miRNA regulating plant responses to abiotic stressors has been developed based on previous studies in more than 30 plant species (Zhang et al., 2013). Knowledge of miRNA-mediated regulatory mechanisms in stress responses has made MRE in 3'UTR as potential targets for modulating cellular stress responses and disease outcomes.

3.3. Stress-induced RNAs (tiRNAs)

These are the novel class of small non-coding RNAs derived from the cleavage of mature cytoplasmic tRNAs in their anticodon loop by the ribonuclease angiogenin (ANG). Different stress conditions (oxidative stress, heat shock, UV irradiation) activate ANG proteins. Among cleaved products of the tRNA, 5' halves derived from $tRNA^{Ala}$ and $tRNA^{Cys}$ were found responsible for the inhibition of translation (Li and Hu, 2012). tiRNAs interfere with the assembly of the cap-binding complex eIF4F and inhibit global protein synthesis as a part of the cellular stress response. The 5' oligogauanidine motif of tiRNA and YB1 protein are essential for inhibiting the translation by the assembly of SG in a phospho-eIF2α-independent manner (Ivanov et al., 2011). The induction of tiRNA by ANG may be determined by the type and intensity of stressors, indicating the significance of these small non-coding RNAs in cellular stress responses. It was also found that tiRNAs inhibit stress-induced apoptosis by directly binding to the cytochrome c (Cyt c) released from the mitochondria (Saikia et al., 2014). This may be an adaptive strategy of the cells during stressful events. However, the precise molecular mechanisms of tiRNA functions, their binding proteins, and relative abundance are yet to be determined.

3.4. Novel UTR mechanisms in cellular stress responses

Apart from the known 5' UTR regulatory elements in the transcripts of stress induced proteins, novel mechanisms have been identified. It was found that heat stress induces adenosine residue methylation (m^6A) in the 5'UTR of Hsp70 mRNA for their selective cap-independent translation (Zhou et al., 2015). A single 5'UTR m^6A directly binds to the eukaryotic initiation factor 3 (eIF3), which is sufficient to recruit the 43 S complex to initiate translation in the absence of the cap-binding factor eIF4E (Meyer et al., 2015). This mechanism explains how post-transcriptional modifications in 5'UTRs facilitate the preferential synthesis of stress-induced proteins. Another novel mechanism of selective translation of essential proteins was observed in the mitochondrial genes during nutritional stresses. These mitochondrial genes contain a cis-acting element TISU (Translation Initiator of Short 5'UTR), present between transcription start sites up to position +30. Eukaryotic initiation factors such as eIF1 and eIF4GI interact with the TISU elements to confer resistance to nutrition stress-induced translation inhibition (Sinvani et al., 2015). Computational methods using partial least square (PLS) regression models, and subsequent experimental characterization of a series of 5'UTR mutants, revealed the presence of cis-regulatory signatures responsible for heat stress-regulated mRNA translation in *A. thaliana* (Matsuura et al., 2013).

In addition to alternative translation initiations, novel mechanisms were also observed in the regulation of mRNA half-life under stress conditions. Cellular mechanisms that decide cytoprotective or apoptotic effects regulate pro/anti-apoptotic mRNA half-life through their 3'UTR. Cleavage and polyadenylation of 3'UTR are essential for maturation of nascent transcripts. Alternative cleavage and polyadenylation (APA) mechanism is another layer in the regulation of gene expression. Selective alternative polyadenylation (APA) facilitates Hsp70.3 expression by enhancing the transcript half-life under stress conditions through the removal of inhibitory regulatory elements from the 3′UTR (Kraynik et al., 2015). Trans-acting factors interacting with the 3'UTR to distinctly regulate translation is currently attracting greater attention. The GAIT (interferon [IFN]-γ-activated inhibitor of translation) system could be one such mechanism. A heterotetrameric complex, GAIT binds to the split stem-loop element in the 3′UTR of target mRNAs to prevent their translation (Jia et al., 2013). In hypoxic stress response, a trans-acting factor, hnRNP L (heterogeneous nuclear ribonucleoprotein), binds to a CA-rich motif near the GAIT targetand prevents its inhibitory effect on VEGF translation (Ray et al., 2008). Significantly, there may be other more complex mechanisms of trans-acting proteins targeting 3' UTR region that regulate translation. Hsp27 interacts with the 3'UTR regulatory elements of pro-apoptotic Bim transcripts and prevents its translation. This repression of Bim mRNA translation through binding to the 3'UTR constitutes a novel cytoprotective mechanism of Hsp27 during stress in the neurons (Dávila et al., 2014). In another distinct mechanism, mRNA containing inverted repeated Alu elements (IRAlus) in their 3' UTRs are retained within the nucleus by paraspeckle-associated protein complexes containing p54 (nrb). However, during certain cellular stresses, CARM1 (coactivator-associated arginine methyltransferase 1) methylates the coiled-coil domain of p54 (nrb) to mediate mRNA transport to the cytoplasm and facilitate their translation (Hu et al., 2015).

4. Conclusions and future directions

Significant advances have been made in our understanding of translation reprogramming during cellular stress physiology. Post-transcriptional regulation mediated by UTRs is an effective mechanism that can quickly adjust the rate of protein synthesis in response to environmental stimuli. Results of several experiments have established the primary role of the RNA motifs in UTRs. Stress-induced repression of global protein synthesis for energy conservation is often accompanied by the selective translation of proteins that are vital for cell survival and recovery. IRES, present in 5'UTRs, provide exit routes to certain transcripts from the inhibited cap-dependent step and determine cell fate decisions leading to either stress adaptation or apoptosis. Diverse higher-order RNA structures and their interacting proteins are suggested in dynamic IRES-mediated cap-independent initiations. The IRES phenomenon is not completely clear but many mechanistic details have emerged recently which not only give insights into translation reprogramming but may also provide attractive targets to develop potential therapeutic strategies (Komar and Hatzoglou, 2015). uORFs represent other regulatory RNA motifs in the 5'UTR that facilitate translation from the principal ORF in pathophysiological stress conditions. Re-initiation is considered as the major mechanism of uORF-mediated regulation; however recent studies have indicated the presence of several other mechanisms including engaging IRES and trans-acting factors which are not well defined. The fact that many human diseases are associated with polymorphisms that alter uORFs indicates the importance of these elements (Barbosa et al., 2013). Further characterization of uORFs may help in developing prognostic/diagnostic markers including novel therapeutic targets for their associated diseases.

The 3'UTR motifs including ARE and MRE have been found to influence the reversible modification and regulation of mRNA half-life in cellular stress responses. By associating with different AUBPs, ARE determine the localization of RNAs and their half-life. Recent findings show how the stalled transcripts are resurrected after a period of accumulation in SG. Our knowledge of miRNA-functions has recently been improved with the studies recording miRNA expression profiles under different stress conditions. The 3' UTRs of the transcripts encoding proteins involved in stress responses confirmed multiple MRE motifs, indicating the prevalence of widespread miRNA-mediated regulation.

Survey of structural and functional aspects of UTRs indicates the presence of different RNA motifs along with their binding proteins. This overriding complex network leads to homeostasis and maintenance of health even when cells encounter environmental insults. Despite emerging details of these mechanisms, our understanding of translation reprogramming is far from complete. Applications of recent technological advances such as RNA sequencing, ribosome profiling and genome editing methods in model organisms may identify other RNA motifs in the UTR and their associated mechanisms. The growing body of evidence suggests that during stress responses, deregulation of translation reprogramming causes abnormal cell behaviour, leading to diseases especially cancers. Future understanding of translational plasticity during cellular stress responses can be expected to facilitate novel developments and applications in physiology and medicine.

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