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Abstract

Cells are exposed to various intrinsic and extrinsic stresses in both physiological and pathological conditions. To adapt to those conditions, cells have evolved various mechanisms to cope with the disturbances in protein demand, largely through the Unfolded Protein Response (UPR) in the Endoplasmic Reticulum (ER), but also through the Integrated Stress Response (ISR). Both responses initiate downstream signaling to transcription factors that, in turn, trigger adaptive programs and/or in the case of prolonged stress, cell death mechanisms. Recently, non-coding RNAs, including microRNA and long non-coding RNA, have emerged as key players in the stress responses. These non-coding RNAs act as both regulators and effectors of the UPR, and fine-tune the output of the stress signaling pathways. Although much is known about the UPR and the cross-talk that exists between pathways, the contribution of small non-coding RNA has not been fully assessed. Herein we bring together and review the current known functions of non-coding RNA in regulating adaptive pathways in both physiological and pathophysiological conditions, illustrating how they operate within the known UPR functions and contribute to diverse cellular outcomes.

Introduction

As the starting point for production and modification of secretory and transmembrane proteins which account for about 20-30% of all proteins produced in the cell, the endoplasmic reticulum (ER), represents a fundamental part of the protein homeostasis network (11). The latter integrates cellular processes that govern the proteome through protein synthesis, degradation, folding, modification and localization (4). Within the ER, the involvement of molecular machines ensuring protein folding, quality control, export and clearance ensure the correct balance between the cellular demand for secretory and transmembrane protein production and the ER capacity to cope with it (36). When this balance is altered, a so-called ER stress is triggered and the unfolded protein response (UPR) is activated to primarily attenuate protein translation, resolve the presence of misfolded/unfolded proteins and induce production of chaperone proteins (44). If the stress cannot be resolved, the UPR signaling outputs will result in the activation of cell death pathways. Although not entirely localized to the ER, other cellular processes such as nonsense-mediated decay (NMD) and the integrated stress response (ISR) also have an impact on ER protein homeostasis. In recent years, numerous studies have uncovered the existence of an additional layer of regulation in these process that is achieved by miRNA and lncRNA. Cell stress pathways are areas of active investigation and the addition of regulatory RNA pathways enhance our understanding of these mechanisms. The current release of miRbase, version 21, lists over 28,000 known miRNAs (55) and given that these numbers are expected to increase, it raises the possibility that there are multiple undiscovered miRNAs that may also regulate cellular stress pathways. This review presents the currently identified non-coding RNA elements of the UPR and ISR.

The Unfolded Protein Response (UPR) and the Integrated Stress Response (ISR)

The UPR is orchestrated by three ER transmembrane sensors; activating transcription factor 6 (ATF6), protein kinase R-like ER kinase (PERK) and inositol-requiring enzyme 1 (IRE1). The three UPR sensors are maintained inactive through the binding of GRP78/BiP to their ER luminal domains. Accumulation of misfolded proteins in the ER promotes GRP78/BiP dissociation from the sensors thereby leading to their activation and that of their downstream signaling (**Figure 1**). These signaling events aim at restoring ER proteostasis through cellular reprogramming

mechanisms but if this fails, cell death will be triggered. The three UPR sensors are activated through different mechanisms and their activation yields specific biological outcomes.

ATF6 is a transmembrane transcription factor that contains a cytosolic bZIP domain. The ATF6 luminal domain contains Golgi localization sequences that are uncovered upon GRP78/BiP dissociation (87), along with conserved cysteine residues which allow for export of ATF6 from the ER to the Golgi apparatus by COPII vesicles (75). The protein disulfide isomerase 5 (PDIA5) is essential for ATF6 activation and transport to the Golgi through modulation of ATF6 disulfide bonds (45). In the Golgi, ATF6 is cleaved by site-1 and -2 proteases on both sides of the membrane thus releasing the cytosolic ATF6 fragment (ATF6f) that acts as an active transcription factor (19). This transcription factor triggers the expression of ER chaperone genes such as GRP78, GRP94 as well as the unspliced form of XBP1 and, in a heterodimer with XBP1, expression of genes associated with endoplasmic reticulum-associated degradation (ERAD) (102).

IRE1 is a transmembrane protein with both cytosolic kinase and RNase activities. Two isoforms of IRE1 are found, namely IRE1α and IRE1β, with IRE1α (hereafter referred to as IRE1) ubiquitously expressed and IRE1β restricted to lung and intestine epithelia (68). As with ATF6, IRE1 is under the control of the GRP78 chaperone. Indeed, upon GRP78/BiP dissociation, IRE1 homodimerizes/oligomerizes and is subjected to transautophosphorlyation. This leads to a conformational change of the endoribonuclease domain promoting its activation (82). In addition to GRP78/BiP, PDIA6 (protein disulfide isomerase 6) also regulates IRE1 through the reduction of cysteine residues in the IRE1 luminal domain (31), either stabilizing IRE1 oligomers (35) or selectively attenuating RIDD activity (30). In mammals, IRE1 excises a twenty-six nucleotide fragment from *XBP1* mRNA and the resulting 5’ and 3’ ends are ligated by RtcB ligase (64). The spliced transcript, named *XBP1s*, encodes a transcription factor that triggers the expression of genes coding for ER chaperones and ERAD associated proteins (1). IRE1 RNase also downregulates other RNAs through targeted degradation, in a process known as RIDD (regulated IRE1 dependent decay). RIDD targets mRNAs such as *SPARC*, *PER1* and *BLOC1S1*, along with individual miRNAs and miRNA families (12, 26, 43, 59, 84, 92, 94).

PERK, a transmembrane ER-resident kinase, is also activated upon dissociation from GRP78/BiP, which in turn triggers homodimerization and trans-

autophosphorylation. PDIA6 regulates PERK in a similar manner to IRE1, attenuating PERK activity during ER stress (30, 31). Activated PERK phosphorylates the eukaryotic translation initiation factor 2 alpha (eiF2α), the transcription factors Nrf2 (nuclear factor, erythroid 2-like 2 transcription factor), and FOXO1 (forkhead box O1). It also acts as a lipid kinase by phosphorylating diacylglycerol (DAG) to produce phosphatidic acid (15). EiF2α phosphorylation attenuates general protein translation, but allows the translation of a subset of mRNAs with short open reading frames in the 5'-untranslated region. The *ATF4* transcription factor contains such an ORF so is translated, inducing the transcription of the growth arrest and DNA damage-inducible protein coding gene GADD153 (also known as C/EBP homologous protein - CHOP). CHOP increases transcription of apoptotic genes and leads to cell death (40) on the one hand but also triggers the expression of *GADD34* (67). GADD34 encodes a subunit of the phosphatase PP1c, which targets the dephosphorylation of eiF2α (65), resulting in a negative feedback loop. NRF2, another PERK substrate, is phosphorylated to release it from sequestration in the cytoplasm by KEAP1, allowing NRF2 to enter the nucleus and regulate expression of genes involved in redox metabolism (23).

Beyond its activation upon accumulation of misfolded proteins, the UPR can also be triggered by stress-independent mechanisms. For instance the IRE1-XBP1 axis is activated by Toll-like receptor 4 (TLR4) in macrophages (69) and activation of all three arms of the UPR by VEGF is observed in endothelial cells (51). Other signaling pathways that activate the UPR include the estrogen receptor (3), and epidermal growth factor (105) in a process known as anticipatory UPR activation, where the UPR is activated pre-emptively before the accumulation of improperly folded proteins.

The ISR is a stress response that overlaps with the UPR through the PERK/eiF2α arm. In addition to PERK, three other kinases, activated upon sensing specific alterations, lead to the phosphorylation of eiF2α and activation of downstream signals. These three kinases are respectively, general control nonderepressible 2 (GCN2), heme-regulated inhibitor (HRI) and protein kinase R (PKR) (80). GCN2 responds to cellular stress induced by amino acid depravation by binding to uncharged tRNA and phosphorylating eiF2α (17). HRI is activated by cellular stress in the form of heme deficiency and also from oxidative stress, resulting in activation by auto-phosphorylation, enabling subsequent phosphorylation of eiF2α (63). PKR is activated by binding of double-stranded RNA resulting from viral

infection of the cell; it then undergoes a conformational change that allows it to phosphorylate eiF2α on the same serine residue (serine 51) as the other kinases (33) (**Figure 1**).

Stress responses and control of RNA expression levels

RNA metabolism, through the control of RNA turnover and translation, influences the UPR, as mRNA levels at ER-bound ribosomes dictate the need for increased or decreased folding capacity of the ER, as well as the effects of short RNA species on components of the UPR. One of the cellular mechanisms involved in RNA homeostasis is the nonsense-mediated decay (NMD) pathway. The NMD pathway can degrade the mRNA of several elements of the UPR which leads to attenuation of UPR signaling. The UPR can in turn downregulate NMD, possibly through translation inhibition by phosphorylation of eiF2α (52). NMD also impacts the integrated stress response, as NMD is decreased in hypoxic cells in a phoshpo-eiF2α dependent-manner. NMD also targets the mRNA of components of the ISR such as ATF3, ATF4 and CHOP (34). Another mechanism for regulating RNA expression/turnover or translation is mediated by micro-RNA (miRNA). These are a subset of small non-coding RNA species that arise from RNA transcripts that fold into short hairpin structures (6). Their biogenesis is first mediated by RNA Polymerase II, that produces a long strand of primary miRNA (pri-miRNA) containing stem loop structures adjacent to the miRNA sequence (58). This product is then processed into precursor miRNA (pre-miRNA) by the microprocessor complex, a multi-subunit complex containing the ribonuclease III protein Drosha and a DGCR8 dimer (76). Pre-miRNAs are then exported from the nucleus via exportin-5-RAN-GTP (104) and processed into mature miRNAs in the cytoplasm by the ribonuclease Dicer (54). Mature miRNAs associate with the RNA-induced silencing complex (RISC). The nucleoporin Nup358 assists in the targeting of mRNA to the RISC through association with Argonaute proteins (86) that eject the passenger strand of miRNA and facilitate miRNA-mediated regulation (39). Interestingly NMD and miRNA networks also intersect as the NMD is regulated by miRNA. For example, NMD components *UPF1* and *MLN51* are regulated by miR-128 (14), *SMG1* by miR-125a and -125b isoforms (93) and *SMG5* by miR-433 (50). Finally, another player in RNA homeostasis is the IRE1 homologue RNase L, which degrades RNA in response to viral infection of the cell. RNase L was recently shown to indirectly disrupt the miRNA machinery, which may be an ER-stress independent parallel pathway to RIDD, as

RNase L targets include the mRNA of proteins destined for the ER, i.e., membrane and secreted proteins (85). RNase L itself is regulated by the miR-29 family in a tumor-suppressive manner, consistent with miR-29's role in other cancers (57) (**Table 4**).

Connecting the UPR and miRNA-mediated signaling in disease

Several examples of the interactions between UPR signaling pathways and miRNAs are now available in the literature (**Tables 1&2**). First, although PERK is regulated by only one miRNA; miR-204 (100), its downstream signaling elements are highly regulated by a large number of miRNAs and contribute to diverse processes from apoptosis to cell survival, depending on the context. Moreover, miRNAs modulate and fine-tune the IRE1-XBP1 axis, which in turn is a regulator of miRNA through XBP1s transcription factor activity and the endoribonuclease activity of IRE1. IRE1 itself is regulated by several miRNAs, and can also cleave miRNA through RIDD (miRIDD; **Figure 2**). The IRE1-miRNA network operates across a variety of cellular processes, displaying context-specific effects and crosstalk between UPR sensor pathways. The miRNA-ATF6 network has not been as extensively researched as that of the other two UPR sensors, with only a handful of miRNAs characterized. ATF6 has thus far only one identified effector miRNA; miR-455, which targets calreticulin, providing an additional insight into the UPR interplay with the protein folding machinery (9). As the knowledge of ATF6 biology in general improves, so too should the knowledge of the ATF6-miRNA network. Finally, similar to what is observed at the protein level, there is also evidence of UPR arms cross-talk at the miRNA level, for instance miR-216b, which is regulated by both CHOP and IRE1 (101). To date, miRNA as either effectors or regulators of the UPR (UPR miRNAs) were shown to be associated with numerous physiological and pathological processes that are illustrated below.

UPR miRNAs involved in Diabetes/pancreatic function - PERK activity is instrumental in pancreas development and function (107), therefore it is not surprising to see that many of the miRNAs implicated in pancreatic function and diabetes are also associated with the PERK pathway. In pancreatic beta cells, PERK was shown to be under the control of miR-204, with overexpression of the miRNA enhancing beta cell apoptosis under ER stress conditions. The same miRNA also targets the transcription factor *MafA*, resulting in decreased insulin production, suggesting that one miRNA can operate at multiple levels to alleviate ER stress

(100). In a β-cell lipotoxicity model, miR-34a-5p was shown to be induced by PERK through a p53-dependent mechanism and to target anti-apoptotic *BCL2* and *BCL2L2* (62). CHOP upregulates the expression of miR-379 in diabetic nephropathy, which targets the ER mannosidase-like *EDEM3* mRNA, possibly together with miR-200 family members, thus contributing to the ER stress and clinical features in this disease (53). PERK is not the only arm of the UPR involved in diabetes, as the miR-200 and miR-466 families are degraded by the RIDD function of IRE1 at the pre-miRNA stage in diabetic bone marrow-derived progenitor cells. Defective IRE1 signaling causes the upregulation of these miRNAs and therefore reduced expression of angiopoietin 1, linking RIDD to angiogenesis, a phenomenon altered in diabetes (94).

UPR-associated miRNAs in cardio-vascular functions – UPR/ISR-associated miRNAs were described in many instances in cardiovascular pathophysiology. Indeed in a mouse cardiomyocyte model, ATF6 activation significantly alters the expression levels of thirteen miRNAs. For instance, miR-455, which is down-regulated by ATF6, in turn negatively regulates the expression of the calcium-binding/chaperone protein calreticulin, which is increased in ischemic hearts and is associated with a cytoprotective response (9). While ATF6 controls the expression of miRNAs, it is also a target of miRNA. As such in mouse cardiomyocytes, mirtronic mmu-miR-702 is down-regulated after isoproterenol treatment and targets *ATF6*. Artificial over-expression of miR-702 through the use of miRNA mimics showed that miR-702 has anti-apoptotic effects *in vitro* after isoproterenol treatment (108). A rat model of heart failure revealed that *XBP1* mRNA is a target of miR-214 and miR-30-3p family members in cardiomyocytes, and that these miRNAs are responsible for the dynamic expression of XBP1s protein, which reaches a peak in the early stage of heart failure and decreases afterwards (27). Another study by the same group observed increased miR-214 levels in both serum and cardiac tissue of patients with chronic heart failure, which had an anti-angiogenic effect in a corresponding mouse model. miR-214 controls angiogenesis through suppression of *XBP1* mRNA in endothelial cells, as the XBP1 transcription factor target VEGF is also suppressed (29). *ATF4* mRNA is targeted by miR-1283 in vascular endothelial cells. Introduction of a miRNA mimic decreased vascular endothelial injury markers, whereas miR-1283 inhibition led to increased levels of apoptosis and cardiac tissue damage (42). In vascular smooth muscle cells (SMC), XBP1s downregulates the expression of calponin 1 through increased transcription of miR-1274B, thereby allowing SMC

proliferation. In addition, miR-1274B is also released extracellularly, a possible mechanism for paracrine regulation of proliferation in neighboring SMCs (106). The miR-30 family, which is comprised of six miRNAs with identical seed sequences, is down-regulated during cardiovascular oxidative stress, inhibits *GRP78* and is at least partially negatively regulated by CHOP (18). More specifically, the miR-30 family member, miR-30a, which was found to be decreased in primary cortical neurons after ischemia was also shown to target *GRP78* mRNA. Transfection with miRNA mimics and inhibitors modulated GRP78 protein levels, while the inhibitor displayed a neuroprotective effect *in vivo* (95). In an ischemic stroke model, *GRP78* mRNA is target of two members of the miR-181 family; miR-181a and miR-181b, which repress *GRP78* mRNA through translational repression. Modulation of miR-181 with mimics and inhibitors regulated both GRP78 expression and cell death, while overexpression of the inhibitor diminishes neural damage in an *in vivo* mouse model (79)). Consistent with this result, another study also showed that inhibition of miR-181b demonstrated a cytoprotective effect, through blocking the targeting of the *GRP78* and ubiquitin hydrolase *UCHL1* mRNAs (83). Both strands of the miR-378a hairpin; miR-378a-5p and miR-378a-3p are highly expressed in cardiac cells. To identify potential targets of these miRNAs, a proteomic screen was performed and revealed that both miRNAs target *GRP78* and calumenin mRNA, as well as other mRNAs involved in glycolysis and the cytoskeleton. The protein homeostasis-relevant protein cyclophilin A is also a target of miR-378a-5p (66). As well as targeting components of the UPR, miRNAs also affect other aspects of the proteostasis machinery, such as chaperone proteins and enzymes involved in protein folding. Under oxidative stress conditions, chaperone proteins including Hsp70, Hsc70, calnexin and Galga2 were found to be the target of AP1-regulated miR-17-5p, which led to reduced h-ERG export through the ER and Golgi, a feature of cardiac diseases (96).

UPR-associated miRNAs involved in hepatic functions - Much of the research in ER-related miRNAs in the liver has been performed in hepatocellular carcinoma (HCC) models, thereby introducing a significant bias in all the results obtained. For instance, miR-214, a miRNA down-regulated in HCC through possible NF-κB-dependent mechanisms, was shown to target *XBP1* mRNA and act in a tumor-suppressive manner, as over-expression of miR-214 mimics reduced tumor volume and weight in a mouse model (28). In HCC, bortezomib, the protease inhibitor used in the treatment of multiple myeloma, induced the expression miR-30b-5p and miR-

30c-5p late in the UPR, suggesting that their regulation is mediated by one of the UPR sensors. These miRNAs target eiF2α mRNA and increase cell viability by preventing the apoptotic ATF4-CHOP signaling downstream of eiF2α(48). In addition to cleavage of miRNAs by IRE1 ribonuclease activity, IRE1 is also directly regulated by miRNA. *IRE1* mRNA is targeted in the 5' UTR by miR-1291 in HCC, leading to downregulation of IRE1 expression and the subsequent stabilization of the RIDD substrate glypican-3 mRNA (71). In another HCC study, ER stress induction with the N-glycosylation inhibitor tunicamycin increased the level of miR-663 and treatment with miRNA mimics increased cell proliferation. miR-663 targets *TGFB1* mRNA and has an impact on ER-stress induced apoptosis by acting in a cytoprotective manner (46). Along with direct regulation of UPR components by miRNAs, other proteostasis-relevant targets of miRNAs have been found in HCC. The Golgi-resident protein ER mannosidase I (ERManI) that contributes to glycoprotein quality control, is up-regulated in HCC and is targeted by miR-125b. miR-125b is down-regulated in HCC, so its target ERManI can maintain efficient cancer cell proliferation and transformation phenotypes (81). UPR-miRNA interactions have also been reported in non-HCC studies. For instance, IRE1 RIDD activity has been reported in a liver fibrosis model; pre-miR-150, which in its mature form is stabilized by XBP1s (109), was found to be cleaved by IRE1, reducing the repression of the transcriptional activator c-Myb and enhancing liver fibrosis through alpha smooth muscle actin (α-SMA) expression (43). In Dicer-deficient hepatocytes under thapsigargin or bile acid (deoxycholic acid)-induced stress, ATF6, IRE1 and the GRP78 chaperone are regulated by miR-199a-5p. The AP-1 transcription factor controls the expression of miR-199-5p, which dampens the ER stress response and prevents cell death through inhibition of IRE1 (24). In a model of nonalcoholic fatty liver disease, miR-615-3p is downregulated under palmitate and tunicamycin-induced stress conditions, leading to an increase of its target *CHOP* and an accompanying increase in cell death through lipoapoptosis. However the exact mechanisms regulating the miRNA expression are as yet unknown (72).

UPR miRNAs involved in Respiratory functions – In human airway epithelial cells, the active XBP1s transcription factor induces the expression of miR-346, which in turn represses antigen peptide transporter 1 (*TAP1*) mRNA. This impacts on immunity by reducing MHC I-associated antigen presentation during ER stress (7). In bronchial brushings from cystic fibrosis (CF) patients, miRNAs -145, -221 and -494 expression levels were elevated and were predicted to target the 3' UTR of the UPR

sensor *ATF6*. In a corresponding CF mouse model, increased expression of these miRNAs was also observed, and regulation of ATF6 by miR-221 was confirmed. The effects of ATF6 regulation by miRNA were not examined in this study, but could have an impact on the unfolded protein response in cystic fibrosis (78). As well as targeting UPR components in the liver, other ER-relevant targets of miR-199a have also been described. In monocytes from patients with α1-antitrypsin deficiency-related chronic obstructive pulmonary disease (COPD), miR-199a-5p levels are increased in α1-antitrypsin deficiency and decreased in COPD. This is due to hypermethylation at the miR-199a promoter, which modulates the UPR through its targets including the NF-κB subunits p50 and p65 (41).

UPR miRNAs in nervous system functions – UPR-mediated regulation of miRNA has been observed in many diseases associated with the nervous system including cancers and degenerative diseases. As such, miR-29a is induced by ER stress, possibly by ATF4 and contributes to ER-stress induced apoptosis in neuroblastoma cells and murine primary cortical neurons by repressing the anti-apoptotic BCL-2 family member, MCL-1 (77). miR-210 regulates the ER chaperone protein prolyl 4-hydroxylase, beta polypeptide (P4HB) in glioblastoma. P4HB promotes resistance to the DNA alkylating agent temozolomide and in both cell lines and clinical samples, *P4HB* mRNA and miR-210 show reciprocal expression levels. In clinical samples, miRNA and mRNA expression levels correlate with disease grade, as the worst grade; Grade IV, has the lowest levels of miR-210 and highest of P4HB. Artificial overexpression of miR-210 in cell lines improved responsiveness to temozolomide treatment (56). In irradiation-resistant glioma stem cells, reduced capability to form tumor spheres and increased irradiation tolerance were associated with decreased expression of GRP78 by miR-205. Treatment of the stem cells with pterostilbene increased the level of miR-205 and to recapitulate this increase, treatment with a miR-205 mimic decreased the expression of GRP78/BiP, along with c-Myc, β-catenin and vimentin, reducing stemness and resistance to radiation treatment (47). *GRP78* was also found to be under the control of another miRNA; miR-384-5p. In an in vitro Parkinson's disease model, where rotenone was used to induce cell death, miR-384-5p levels increased and targeted the 3' UTR of *GRP78* mRNA. The results were also validated in primary neurons, with miR-384-5p also showing an increase after rotenone treatment and decreased cell viability upon treatment with miRNA mimics (49). In a mouse model of Alzheimer’s disease, levels of miR-200c correlated with ER stress levels, as miR-200c expression increased

upon ER stress. However, the exact mechanism of its upregulation is unknown. miR-200c, along with other members of the miR-200 family, regulate the tumor suppressor *PTEN*, and displayed a cytoprotective effect during early ER stress while contributing to apoptosis under later, irremediable ER stress (99).

UPR-associated miRNA and other cellular functions

UPR-associated miRNAs and apoptosis/cell survival - All three arms of the UPR are known to influence these processes (44), however the majority of miRNA regulation regarding apoptosis is focused on the PERK signaling pathway. The processes by which these signals lead to apoptosis include a diverse range of biological pathways, so examining the miRNA component(s) can help to clarify their mechanisms and fine tune the balance between the adaptive and terminal UPR. The miR-106b-25 cluster, which is comprised of the miRNAs miR-106b, -93 and -25, is located in an intron of the *MCM7* gene and is therefore under the same regulation i.e., downregulated by the PERK substrates NRF2 and ATF4. Repression of this miRNA cluster is required for ER-stress induced apoptosis, as it normally inhibits the translation of pro-apoptotic *Bim* mRNA (38). Transcription of miR-211 is induced by the PERK pathway in an ATF4/phospho-eiF2α dependent manner, which leads to repression of CHOP by histone medication and ribosome stalling at the promoter and resulting in increased cell survival (21). In addition to regulation by miRNA, CHOP also regulates miRNA expression through its transcription factor activity, with an increase in miR-216b levels after ER stress. In a convergence of two UPR pathways, IRE1 indirectly represses transcription of miR-216b, possibly through CHOP regulation. Upon ER stress activation, miR-216b contributes to the downregulation of c-JUN and modulates ER-stress-induced apoptosis (101). Overexpression of the miR-23a~27a~24-2 cluster induces apoptosis through ER stress-dependent mechanisms by upregulating components of the UPR such as PERK, ATF4 and CHOP. The cluster also acts on calcium signaling by increasing the amount of cytoplasmic Ca^{2+}, which may also contribute to apoptosis by affecting mitochondrial membrane permeability and the release of cytochrome c and AIF (20). *GRP78* mRNA is regulated by the coordinated action of three miRNAs; miR-30d, miR-181a and miR-199a-5p. Transfection of cells with all three of these miRNAs led to reduced GRP78 expression, abrogating its cytoprotective effect and increasing sensitivity to the histone deacetylase inhibitor trichostatin A, as well as reduced tumor growth in an *in vivo* mouse model (88). In addition to regulating *GRP78*, miR-

30 family members also regulate *XBP1*. miR-30c-2-3p contributes to the pro/anti-apoptotic balance of the UPR, as inhibition of the miRNA leads to a decrease in cell death while also demonstrating the cross-talk between the three arms of the UPR as the miRNA itself is regulated a PERK/NF-κB pathway (16). IRE1 is involved in the regulation of miRNA through its kinase domain, as it cleaves miRNAs -17, 34a, 96 and 125b. This event leads to translation of the miR-17 target thioredoxin Interacting Protein (*TXNIP*) and in the case of all four miRNAs, reduces the repression of caspase-2 mRNA (59, 92). In a more detailed study of miR-34a in an acute myeloid leukemia model, treatment with IRE1 RNase and miR-34a inhibitors slightly decreased cell growth, demonstrating that targeting the UPR at multiple levels, i.e. at the enzymatic and miRNA level, could be beneficial in cancer treatment (90).

Other-associated UPR miRNAs - ER/stress-responsive miRNA signaling is involved in a diverse range of cellular processes from the cell cycle to developmental processes (70). The intronic miRNA, miR-708 and the gene in which it is located, *Odz4*, are regulated by the CHOP transcription factor during ER stress miR-708 is highly expressed in the brain and eye, and represses the vision-relevant target rhodopsin, which may impact on ER protein homeostasis as rhodopsin protein requires processing in the ER (8). In addition to targeting *XBP1* in cardiovascular systems, miR-214 also has other UPR-relevant targets. In a screen to identify miRNA regulators of bone development, high expression of miR-214 was found to inhibit bone formation through targeting *ATF4* mRNA (97). As well as participating in the process of bone formation, miR-214 targets *ATF4* in erythroid cells. miR-214, under the transcriptional control of the PERK substrate NRF2, acts in a cytoprotective manner after oxidative stress. miR-214 levels decrease, allowing for expression of ATF4, while another miR-214 target, the histone modifier EZH2, represses pro-apoptotic Bim, contributing to the cytoprotective effect of miR-214 (32). Dai *et al* profiled the expression of different miRNAs in response to thapsigargin-induced ER stress and found increased expression of miR-221-3p and miR-452-5p, as well as a decrease in miR-423-5p. *CDKN1B* was then identified as a target of miR-452-5p and miR-221-3p, whereas miR-423-5p targets *CDKN1A*, potentially illustrating cross-talk between the UPR and other cellular processes such as the cell cycle (25). Also under thapsigargin-induced ER stress, the PERK branch of the UPR controls the increased expression of miR-663a through unknown mechanisms. miR-663a targets *PLOD3* mRNA, and negatively impacts type IV collagen secretion through repression of lysyl hydroxylase 3 activity at the mRNA

level (2). In tubular renal cells, miR-205 expression is decreased by ER stress, thus increasing levels of its target mRNA, the hypoxia-inducible factor prolyl hydroxylase *EGLN2*. This sensitizes cells to stress by negatively regulating the EGLN2 targets ATF4, HIF1α and HIF2α (73). XBP1s transcription factor activity unrelated to the canonical UPR signaling pathways has been reported in developmental processes. In the process of adipogenesis, XBP1s has been shown to suppress *WNT10B* by up-regulating transcription of its inhibitory miRNA; miR-148a (22). In the context of myofibre development and differentiation, miR-181a-5p was increased upon ER stress and was again shown to target *GRP78* mRNA, promoting apoptosis and decreasing cell viability, along with indirectly regulating the expression of myogenic related genes (98). The miR-424(322)-503 cluster is repressed by the PERK pathway during ER stress and negatively regulates the transcription of ATF6 through miR-424 binding to the 3' UTR of *ATF6* mRNA. The miRNA cluster also positively regulates IRE1 RIDD activity through indirect mechanisms (37). miR-322 expression is lowered after thapsigargin-induced ER calcium depletion, however it is unclear if this is through RIDD activity by IRE1 or by the action of IRE1 downstream factors. The repression of miR-322 allows for the expression of its target *PDIA6*, which then regulates IRE1 and PERK activity at a protein level (35).

Long non-coding RNA and ER homeostasis

Long non-coding RNAs (lncRNA), molecules over 200 base pairs long, are also involved in regulation of protein homeostasis. LncRNAs are genomically abundant regulatory RNA molecules involved in processes as diverse as post-transcriptional, translational and post-translational regulation (35). The processes by which lncRNAs are involved in protein homeostasis are somewhat analogous to miRNA, in that their levels can increase or decrease upon ER stress, depending on their function, to influence cell fate under stressed conditions (**Table 3**). For instance, the lncRNA gadd7 is increased following induction of oxidative stress in CHO cells, acts a general regulator of oxidative stress and is essential for palmitate-induced ER stress (13). In addition to regulation by miR-455, the ER protein calreticulin is also under the regulation of a lncRNA that shares a bidirectional promoter with the RB1 gene; ncRNA-RB1. When ncRNA-RB1 is depleted, calreticulin levels also decrease. Cell surface localized calreticulin functions as a signal in immunogenic cell death, so decreased levels of ncRNA-RB1 results in reduced uptake by macrophages, providing an insight into how cancer cells can escape this death mechanism (74).

Another lncRNA, lincRNA-p21, functions as a tumor suppressor in hepatocellular carcinoma through activation of ER stress pathways (103), while the lncRNA Malat1 showed increased expression upon flavivirus infection through PERK-dependent transcriptional activity. Interestingly, Malat1 itself is subject to miRNA regulation, demonstrating the complexity of RNA regulation, particularly under ER stress (10). The lncRNA TUG1 was identified through RNASeq as a lncRNA that may reduce apoptosis through inhibition of ER stress in cold-induced liver cell damage, as overexpression of TUG1 reduced expression of UPR components such as GRP78, PERK and CHOP (89). The CHOP regulated miRNA-379 is part of a megacluster of miRNAs present within a lncRNA transcript, lnc-MGC, and provides a link between lncRNA and miRNA in the context of ER stress. The cluster of approximately forty miRNAs display the same regulatory pattern by CHOP and together target genes involved in ERAD and protein synthesis (53). This indicates that the extent of RNA-mediated regulation of the UPR is far more complex than anticipated and involves mRNA, miRNA, lncRNA. A systematic analysis of the interconnectivity of these RNA signaling networks will require extensive work in various experimental models before being able to propose an integrated view of the underlying mechanisms and their biological outcomes.

Conclusions and perspectives

It is clear from the evidence presented in this review that the contributions of miRNA and lncRNA to the cellular stress responses represent an important regulatory role in addition to the already recognized signaling pathways. These small non-coding RNAs affect a diverse range of normal cellular processes, and when deregulated can result in disease states. Even in the context of miRNA which is active under cellular stress, the effects of these miRNAs are not limited to pathways related to the stress response, but can affect processes as diverse as cell cycle to adipogenesis regulation (**Table 2**). An important point to note is that many of the studies reviewed in this article used animal models, which therefore need to be validated in the human context, as certain miRNAs and miRNA families diverge between humans and other species. The majority of the miRNAs reviewed here were examined in response to cellular stress, such as the chemical stressors tunicamycin or thapsigargin, but also physiological stresses such as hypoxia and nutrient deprivation, which more closely mimic the natural environment. It has been suggested that miRNAs act as buffers to regulate mRNA expression during stress and particularly affect transcription factors

and signaling molecules (60). During stress responses where global translation is shut down through eiF2α phosphorylation, this buffering function may be more important than in normal cellular metabolism. All of the signaling pathways discussed; nonsense-mediated decay, RNase L mediated decay, the UPR and the ISR are all under the regulation of non-coding RNA and in the case of the UPR and ISR, the transcription factors which these processes use to mediate their effects are also found to be under the control of non-coding RNA. The endoplasmic reticulum itself is an important step in the miRNA: mRNA interaction, as a recent report from Barman and Bhattacharyya identified ER-bound polysomes as the site where mRNA associates with Ago2 proteins and miRNA, ultimately resulting in translational repression (5). Much of the research reviewed here examines the role of non-coding RNA in cancer. In the context of cancer, miRNAs can be classified as tumor-suppressive or oncogenic (91), however the cell type and context must be taken into consideration. This holds true for ER protein homeostasis too, as the different miRNAs involved in regulation show different effects, such as miR-199a-5p, which shows a cytoprotective effect when IRE1 is inhibited, yet an apoptotic effect when GRP78 or ATF6 is inhibited (24). As well as the different roles of various miRNA in cancer, mutations in the miRNA biogenesis machinery such as those in Drosha or Dicer, also alter the miRNA expression profiles and therefore gene and protein expression (61).

This article reviews the complex, inter-connected non-coding RNA network involved in the regulation of the UPR. Much of the work to date has been concentrated on the well-established UPR, but other players, such as nonsense-mediated decay are emerging as ER protein homeostasis regulators, as well as the molecular machinery itself. Non-coding RNA regulation of ER protein homeostasis has been discovered in many cellular processes, both physiological and pathological and future work can now concentrate on integrating the role of the identified miRNAs and lncRNAs, as well as those yet to be identified, into the established networks as a definite additional layer of regulation.

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Figure Legends

Fig. 1. The integrated stress response and the unfolded protein response. The UPR sensors are resident in the ER membrane, PERK (blue), and IRE1 (green) have cytoplasmic kinase domains, with an additional RNase domain present in IRE1. ATF6 (red) also has a cytoplasmic domain, which is processed in the Golgi apparatus upon ER stress. The UPR induces transcription factors, represented here by ATF6f, XBP1s, NRF2, CHOP and ATF4. The ISR (grey) and UPR converge at the PERK sensor, with the cytoplasmic and/or nuclear ISR responding to different stressors than those of the UPR. PERK halts global translation through phosphorylation of serine 51 of the Eukaryotic Initiation Factor 2α sub unit

Fig. 2. miRNAs associated with the UPR. GRP78 (purple) is regulated by nine miRNAs, with three working co-operatively. The PERK sensor (blue) is regulated by one miRNA, and regulates several miRNAs through its downstream pathways. IRE1 (green) is regulated by several miRNAs, regulates miRNA through the transcription factor Xbp1s and degrades miRNA through its RNase activity. ATF6 (red) is also regulated by several miRNAs, with one downstream effector miRNA. Where known, the mRNA target(s) of the miRNAs are shown as enclosed circles. For simplicity, cross-talk mechanisms are not shown

Table 1: miRNAs directly associated with the UPR/ISR. miRNAs that regulate the stress sensors are defined as regulators. miRNAs regulated either by the sensor themselves or by pathways downstream of the sensors are defined as effectors. GRP78 has only regulator miRNAs

PERK/ISR	**IRE1**	**ATF6**	**GRP78**
Regulators of the UPR/ISR			
miR-204 (100)	miR-30-3p family (27)	miR-145 (78)	miR-30a (95)
	miR-30c-2-3p (16)	miR-199a-5p (24)	miR-30d (88)
	miR-199a-5p (24)	miR-221 (78)	miR-30 family (18)
	miR-214 (27–29)	miR-424(322)-503 cluster (37)	miR-181a (88)
	miR-424(322)-503 cluster (37)	miR-494 (78)	miR-181b (83)
	miR-1291 (71)	miR-702 (108)	miR-199a-5p (88)
			miR-205 (47)
			miR-378a-3p (66)
			miR-378a-5p (66)
			miR-384-5p (49)
Effectors of the UPR/ISR			
miR-29a (77)	miR-17 (59, 92)	miR-455 (9)	
miR-30c-2-3p (16)	miR-34a (92)		
miR-30 family (18)	miR-96 (92)		
miR-34a-5p (62)	miR-125b (92)		
miR-106b-25 cluster (38)	miR-148a (22)		
miR-211 (21)	miR-150 (43)		
miR-214 (32, 97)	miR-200 family (94)		
miR-216b (101)	miR-346 (7)		
miR-379 (53)	miR-466 family (94)		
miR-424(322)-503 cluster (37)	miR-1274B (106)		
miR-663a (2)			
miR-708 (8)			
miR-1283 (42)			

Table 2: miRNAs that regulate proteostasis, whether they are up-regulated or down-regulated in the experimental model, their targets, the context in which the miRNA was studied and the outcome when the miRNA/lncRNA carries out its function. Where no specific model was used, the cell type/stressor is indicated. Where both up- and down-regulation occur, time course or adjacent tissues were both studied. Where nwither regulation is indicated, miRNA levels were artificially modulated.

miRNA	Up/Down	Target(s)	Cell type/Disease model	Effect/Outcome	Reference
miR-17	Down	CASP2	T-REx-293	Caspase 2 translation	(92)
	Down	TXNIP	MEF	Inflammasome and caspase 1 activation	(59)
miR-17-5p	Up	Hsp70	Oxidative stress	Disrupted h-ERG activity	(96)
		Hsc70			
		Calnexin			
		Galga2			
miR-29a	Up	Mcl-1	Neurons	Pro-apoptotic	(77)
miR-30 family	Down	GRP78	Cardiovascular oxidative stress	Weakened ER stress response	(18)
miR-30-3p family	Both	XBP1	Cardiomyocytes	Decreased Xbp1 and VEGF expression	(27)
miR-30a	Down	GRP78	Ischemia	Apoptosis	(95)
miR-30b-5p	Up	eiF2α	Bortezomib treatment	Increased cell viability	(48)
miR-30c-5p					
miR-30c-2-3p	Up	XBP1	Tunicamycin treatment	Apoptosis	(16)
miR-30d	Down	GRP78	Trichostatin A treatment	Apoptosis	(88)
miR-34a	Down	CASP2	T-REx-293	Caspase 2 translation	(92)
miR-34a-5p	Up	BCL-2	Pancreatic β-cell lipotoxicity	Decrease in BCL-2 and BCL2L2 protein expression	(62)
		BCL2L2			
miR-96	Down	CASP2	T-REx-293	Caspase 2 translation	(92)
miR-106b-25 cluster	Down	Bim	ER stress	Decreased apoptosis	(38)
miR-125b	Down	CASP2	T-REx-293	Caspase 2 translation	(92)
	Down	ERManI	Hepatocellular carcinoma	Decreased transformation, proliferation and invasion	(81)

miR-145	Up	ATF6	Cystic fibrosis	Decreased ATF6 levels	(78)
miR-148a	Up	Wnt10b	Adipogenesis	Differentiation through suppression of Wnt10b	(22)
miR-150	Down	cMyb	Fibrosis	Increased fibrosis through α-SMA activation	(43)
miR-181a	Up	GRP78	Ischemic stroke	Increased cell death	(79)
	Down		Trichostatin A treatment	Apoptosis	(88)
	Up		Myogenic differentiation	Apoptosis	(98)
miR-181b	Down	GRP78	Ischemic stroke	Decreased cell survival	(83)
miR-199a-5p	Down	p50, p60	AAT-deficient monocytes	Regulates ER stress response	(41)
	Up	ATF6	Hepatic ER stress	Apoptosis	(24)
	Up	IRE1	Hepatic ER stress	Cytoprotection	(24)
	Up	GRP78	Hepatic ER stress	Apoptosis	(24)
	Down		Trichostatin A treatment	Apoptosis	(88)
miR-200 family	Down	ANGPT1	Diabetic wound healing	Impaired angiogenesis	(94)
miR-200c	Up	PTEN	Alzheimer's disease	Cytoprotective	(99)
miR-204	−	PERK	Pancreatic β-cells	Intensifies ER-stress induced apoptosis	(100)
		MafA		Inhibits insulin transcription	
miR-205	Down	EGLN2	Renal tubular cells	Cytoprotection	(73)
	Down	GRP78	Glioma stem cells	Decrease in GRP78, c-Myc, β-catenin and vimentin	(47)
miR-210	Down	P4HB	Temozolomide-resistant glioblastoma	Reduced chemoresistance	(56)
miR-211	Both	CHOP	Mammary carcinoma, lymphoma	Cell survival	(21)
miR-214	Up	ATF4	Osteoblasts	Decreased bone formation	(97)
	Down		Erythroid cells	Cytoprotection	(32)
	Down	XBP1	Hepatocellular carcinoma	Tumor suppressive	(28)
	Up		Heart failure	Anti-angiogenic	(27, 29)
miR-216b	Up	c-Jun	NIH3T3, MEF, HEK293T, U2OS	Sensitivity to ER stress-induced apoptosis	(101)
miR-221	Up	ATF6	Cystic fibrosis	Decreased ATF6 levels	(78)

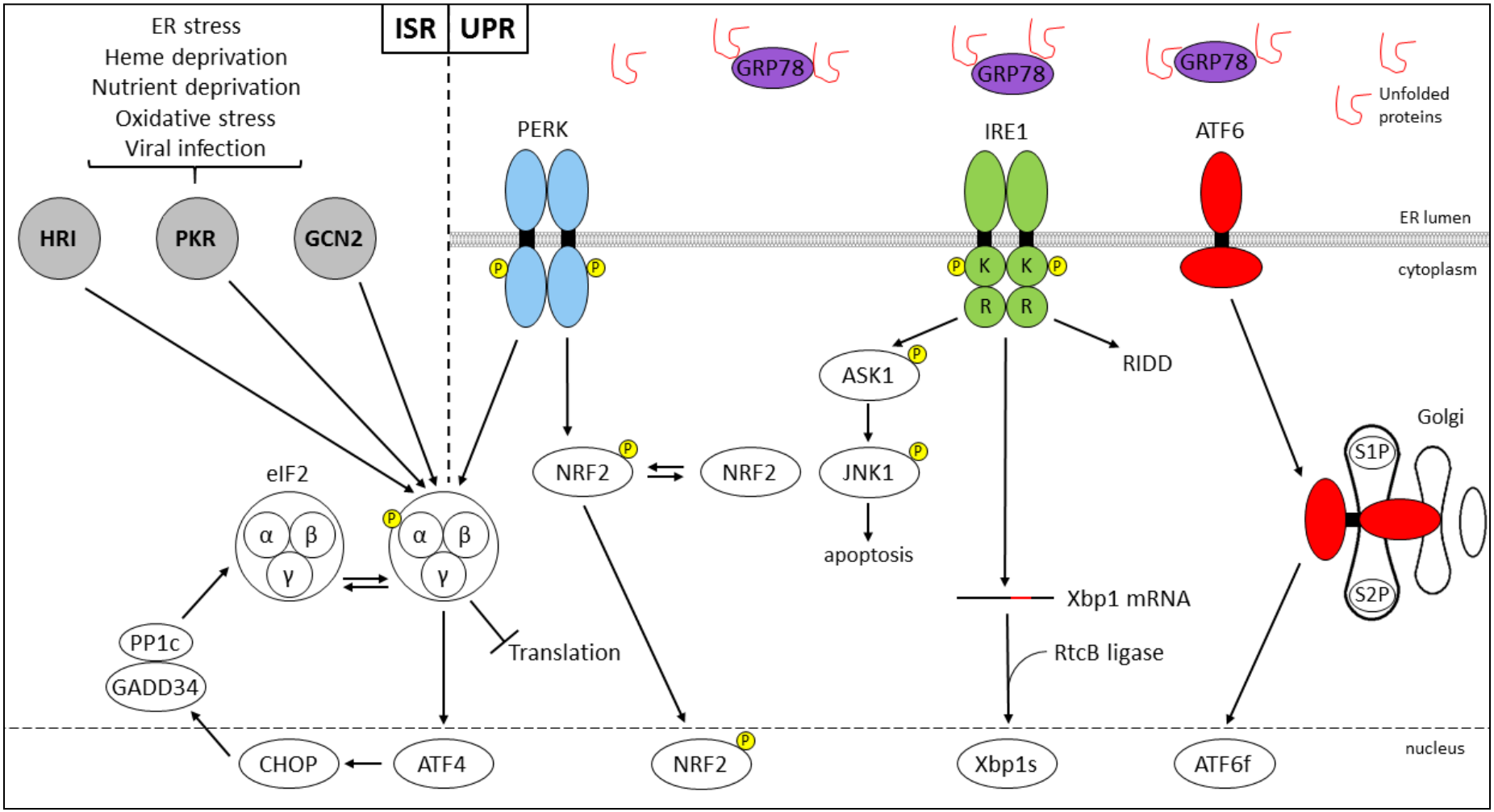
miR-221-3p	Down	CDKN1B	HeLa/HEK293	Decreased CDKN1B protein levels	(25)
miR-322	Down	PDIA6	Calcium homeostasis	Sustained UPR response	(35)
miR-346	Up	TAP1	Airway epithelium	Reduced MHC I-associated antigen presentation	(7)
miR-378a-3p	–	GRP78	Cardiomyocyte energy metabolism	Decreased GRP78, calumenin and GRP94 expression	(66)
		CALU			
miR-378a-5p	–	GRP78	Cardiomyocyte energy metabolism	Decreased GRP78, calumenin, PPIA and GRP94 expression	(66)
		CALU			
		PPIA			
miR-379	Up	EDEM3	Diabetic nephropathy	Fibrosis, hypertrophy	(53)
miR-384-5p	Up	GRP78	Parkinson's disease	Decreased cell viability	(49)
miR-423-5p	Up	CDKN1A	HeLa/HEK293	Decreased CDKN1A protein levels	(25)
miR-424(322)-503 cluster	Down	ATF6	HEK 293T/H9c2/MEFs	Decrease in ATF6 mRNA, enhanced RIDD activity	(37)
miR-452-5p	Down	CDKN1B	HeLa/HEK293	Decreased CDKN1B protein levels	(25)
miR-455	Down	CALR	Ischemia	Cytoprotection	(9)
miR-466 family	Down	ANGPT1	Diabetic wound healing	Impaired angiogenesis	(94)
miR-494	Up	ATF6	Cystic fibrosis	Decreased ATF6 levels	(78)
miR-615-3p	Down	CHOP	Hepatocyte lipoapoptosis	Cell survival	(72)
miR-663	Up	TGFB1	Hepatocellular carcinoma	Apoptosis	(46)
miR-663a	Up	PLOD3	HeLa/Huh7	Reduced collagen secretion	(2)
miR-702	Down	ATF6	Mouse cardiac tissue	Cell survival	(108)
miR-708	Up	RHO	Vision	Decreased rhodopsin production	(8)
miR-1283	Up	ATF4	Vascular endothelium	Cytoprotection	(42)
miR-1274B	Up	CNN1	Vascular injury	Smooth muscle cell proliferation	(106)
miR-1291	Down	IRE1	Hepatocellular carcinoma	Glypican-3 expression	(71)

Table 3: lncRNAs that regulate proteostasis, their targets, the context in which the miRNA was studied and the outcome when the miRNA/lncRNA carries out its function. Where no specific model was used, the cell type/stressor is indicated.

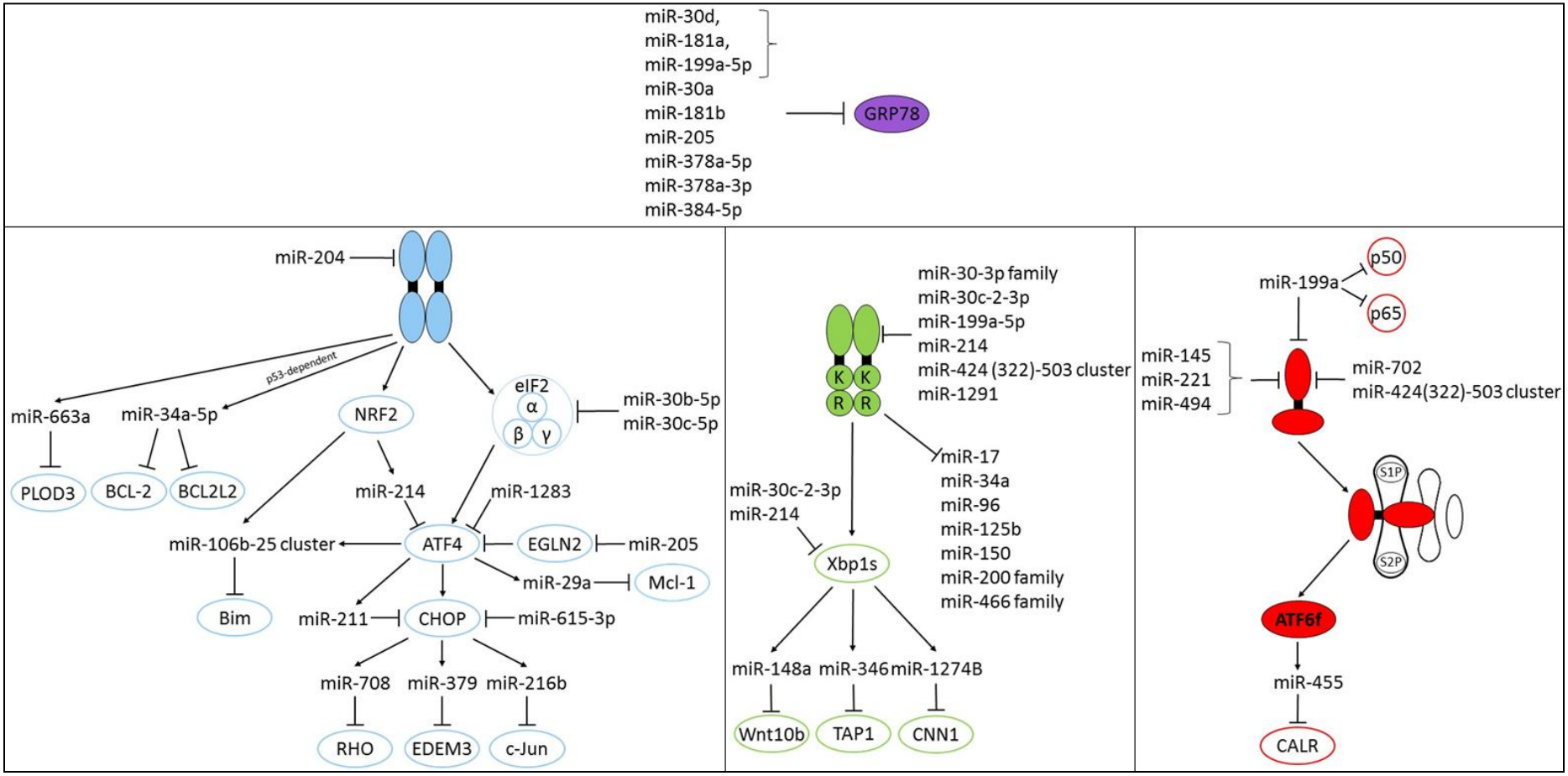
lncRNA	Cell type/Disease model	Effect/Outcome	Reference
gadd7	Oxidative stress in CHO cells	ER stress and cell death	(13)
lincRNA-p21	Hepatocellular carcinoma	Activation of ER stress	(103)
lnc-MGC	Diabetic nephropathy	Fibrosis and hypertrophy	(53)
Malat1	Flavivirus infection	Transcriptional upregulation of Malat1	(10)
ncRNA-RB1	Calreticulin regulation	Immunogenic cell death	(74)
TUG1	Cold-induced injury in the liver	Cytoprotection	(89)

Table 4: miRNAs that indirectly regulate proteostasis through other processes, their targets, the context in which the miRNA was studied and the outcome when the miRNA/lncRNA carries out its function. Where no specific model was used, the cell type/stressor is indicated.

miRNA	Target(s)	Cell type/Disease model	Effect/Outcome	Reference
miR-29 family	RNase L	CML	Tumor suppressive	(57)
miR-125	SMG1	HeLa, HEK 293T	Suppression of NMD pathway	(93)
	MLN51			
miR-128	UPF1	Brain development	Upregulation of NMD substrates	(14)
miR-433	SMG5	Nonsense-mediated decay	Decreased NMD activity	(50)



McMahon et al. Fig. 1



McMahon et al. Fig. 2