miRNAs at the interface of cellular stress and disease

Anna Emde & Eran Hornstein*

Abstract

miRNAs (miRNAs) are a family of small, non-coding RNAs, which provides broad silencing activity of mRNA targets in a sequence-dependent fashion. This review explores the hypothesis that the miRNA machinery is intimately linked with the cellular stress pathway and apparatus. Stress signaling potentially alters the function of the miRNA-bioprocessing core components and decompensates regulation. In addition, dysregulation of miRNA activity renders the cell more prone to stress and emerges as a new pathway for age-related insults and diseases, such as neurodegeneration.

Keywords cellular stress; dicer; disease; micrornas; stress granules

Introduction

miRNAs

miRNAs are genome-encoded small RNAs that mediate post-transcriptional silencing. Considering hundreds of miRNA genes, each with many dozens of targets, regulation by miRNAs is very broad and met in any cellular activity in health or in disease (Bushati & Cohen, 2008; Bartel, 2009; Carthew & Sontheimer, 2009; Fabian et al., 2010). miRNA precursors are processed in two steps (Fig 1). The initial miRNA transcript (pri-miRNA) is subjected to a nuclear processing by the Drosha–DGCR8 ‘microprocessor’ complex. The resulting intermediate precursor (pre-miRNA) is exported to the cytoplasm and then further identified and cut by Dicer, yielding a 22-nt mature miRNA (Gregory et al., 2005). Partners of Dicer are required for efficient pre-miRNA processing and include Argonaute (AGO), protein kinase interferon-inducible double-stranded RNA-dependent activator (Pact) and TAR RNA-binding protein (Trbp; Chendrimada et al., 2005; Haase et al., 2005; Diederichs & Haber, 2007; Koscianska et al., 2011). Dicer and its co-factors load the mature miRNA onto AGO in the RNA-induced silencing complex (RISC), providing sequence-specific silencing activity.

Argonaute RISC catalytic component 2 (AGO2) has dual functions in the processing of miRNA precursors and in target silencing. First, AGO2 functions as a Dicer co-factor in pre-miRNA processing, as part of the RISC-loading complex. Next, AGO2 is loaded with a guide miRNA strand, making an active RISC (Chendrimada et al., 2005; Gregory et al., 2005). Once programmed with a particular miRNA sequence, RISC acts as an effector that facilitates miRNA-dependent mRNA silencing (Fig 1). Therefore, miRNA processing and target-RNA repression are physically and functionally interlinked by sharing many common protein components.

miRNA circuitry buffers unwanted gene expression, and loss of miRNA activity enables drift from normal cellular function (Hornstein & Shomron, 2006; Li et al., 2009; Herranz & Cohen, 2010; Mukherji et al., 2011; Pelaez & Carthew, 2012; Cassidy et al., 2013; Siciliano et al., 2013). In recent years, an intimate link between miRNA activity and the cellular stress response has been uncovered and is the focus of this review. We explore the evidence that stress signaling and the miRNA biosynthesis machinery are interlinked at various levels of activity. miRNAs emerge as critical regulators of the stress response, and dysregulation of miRNA expression or activity renders the cell more prone to stress and to its insults.

Stress and stress granule formation

Extreme environmental conditions and chemical stressors invoke a cellular cascade, which reduces the damage and conserves integrity. This adaptive response for coping with stress is executed primarily by transient blockade in translation of most cellular miRNAs and directing cellular RNA metabolism toward damage repair (Ron & Walter, 2007). The phosphorylation of eukaryotic translation initiation factor 2 alpha (eIF2a) is the canonical signal for blocking translation initiation and promoting polysome disassembly. Accordingly, the phosphorylation of eIF2a is controlled by stress-activated kinases, PKR, HRI, PERK, or GCN2 (Chen et al., 1991; Dever et al., 1992; Carroll et al., 1993; Harding et al., 1999).

mRNA from disassembling polysomes is often found in cytoplasmic stress granules (SGs), the structural correlate of the stress response (Kedersha et al., 1999; Anderson & Kedersha, 2006; Anderson & Kedersha, 2008; Buchan & Parker, 2009). SGs are composed of stalled translation preinitiation complexes: 40S ribosomal subunits, translation initiation factors (eIFs) and RNA-binding proteins that are involved in other facets of RNA metabolism (Fig 2). Recruitment of proteins into SGs is regulated and in specific conditions is facilitated by so-called ‘piggyback’
Several RNA-binding proteins that are identified in SGs are encoded by genes that are mutated in different neurodegenerative states, including TAR DNA-binding protein 43 (TDP-43; Liu-Yesucevitz et al., 2010; McDonald et al., 2011), fused in sarcoma (FUS; Bosco et al., 2010; Vance et al., 2013), heterogeneous nuclear ribonucleoprotein A1 (hnRNPA1; Kim et al., 2013), valosin containing protein (VCP; Johnson et al., 2010; Buchan et al., 2013) and SMN (survival motor neuron 1; Hua & Zhou, 2004). Other SG resident proteins were also linked to the molecular pathogenesis of neurodegeneration, including eukaryotic translation initiation factor 2A (eIF2a; Kim et al., 2014); HuR (Lu et al., 2009); TIA1 (Lu et al., 2009); SMN (Hua & Zhou, 2004); TDP-43 (Liu-Yesucevitz et al., 2010; McDonald et al., 2011); FUS (Bosco et al., 2010; Vance et al., 2013); hnRNPA1 (Kim et al., 2013); ATXN2 (Farg et al., 2013); VCP (Johnson et al., 2010; Buchan et al., 2013); PRMT1 (Tradewell et al., 2012; Yamaguchi & Kitajo, 2012).

The interconnection between miRNAs and the cellular stress response

Association between the Dicer complex and the cellular stress response

Several lines of evidence reveal links between the Dicer complex and the cellular stress response. Stress may be experimentally induced by many reagents. Stressors, including reactive oxygen species (ROS),...
Stress-induced P38/MAPK signaling phosphorylates AGO2 to Dicer and inhibits pre-miRNA processing (Shen et al., 2013). Epidermal growth factor receptor (EGFR) signaling phosphorylates tyrosine 393 under hypoxic conditions, which reduces the binding of AGO2 to Dicer and inhibits pre-miRNA processing (Shen et al., 2013). In addition, stress-induced P38/MAPK signaling phosphorylates AGO2 at Serine 387 (Zeng et al., 2008). Hypoxic stress regulates AGO2 post-translationally as well, via hydroxylation of proline 700 (Qi et al., 2008), which leads to AGO2 SG localization (Wu et al., 2011). Taken together, it appears that various stress signaling cascades control AGO2 activity and contribute to AGO2 translocation into SGs and to attenuation of miRNA processing. However, further mechanistic studies will be required for understanding of the full picture.

PACT and TRBP are two co-factors of Dicer, which are engaged in the cellular stress response via direct interaction with PKR. PKR is a dsRNA-dependent serine/threonine protein kinase sensor of viral dsRNA that phosphorylates eIF2a on Ser51, thereby causing global reduction of protein synthesis (Taylor et al., 2005; Garcia et al., 2006). PACT and TRBP both contribute to Dicer complex functions but possess distinct, non-redundant, activities (Lee et al., 2006). PACT and TRBP participate at multiple levels of stress signaling, as summarized in Fig 3, substantiating the connection between the Dicer/miRNA-RISC loading complex and the stress response.

Stress signaling alters AGO2 function by post-translational modifications, and these are suggested to impact RISC and Dicer activity. Epidermal growth factor receptor (EGFR) signaling phosphorylates tyrosine 393 under hypoxic conditions, which reduces the binding of AGO2 to Dicer and inhibits pre-miRNA processing (Shen et al., 2013). In addition, stress-induced P38/MAPK signaling phosphorylates AGO2 at Serine 387 (Zeng et al., 2008). Hypoxic stress regulates AGO2, phorbol ester, UV radiation or type I interferon, cause a reduction in the expression of Dicer (Wiesen & Tomasi, 2009; Mori et al., 2012). These changes in Dicer levels appear to be particularly relevant for further coping with stress, since loss of Dicer function reduces stress tolerance, whereas Dicer over-expression confers stress resistance, at least in invertebrates (Lim et al., 2011; Mori et al., 2012). Therefore, Dicer activity contributes to stress resistance. In addition, Dicer co-factors AGO, PACT and TRBP participate at multiple levels of stress signaling, as summarized in Fig 3, substantiating the connection between the Dicer/miRNA-RISC loading complex and the stress response.

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**Stress granules and the miRNA machinery are interlinked**

SGs recruit proteins, which are involved in miRNA regulation pathways. This further suggests that SGs are integrated with miRNA-induced translational silencing pathways. Indeed, fragile X mental retardation protein (Caudy et al., 2002; Jin et al., 2004; Li et al., 2008) and Pupb1 (Moretti et al., 2012) interact with the miRNA machinery. Furthermore, AGO2 and PACT are recruited into stress granules, a process that depends at least partially on HSP90 activity (Leung et al., 2006; Pare et al., 2009; Johnston et al., 2010). In this context, Leung and Sharp suggested that AGO translocation into SGs may reflect a dynamic change in its activity (Leung et al., 2006). Stress response is extended also to the regulation of RISC activity, by poly-ADP ribosylation and probably other mechanisms. Additional investigations will substantiate initial reports in this field that focus on specific subsets of
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mRNAs (Leung et al, 2011; Karginov & Hannon, 2013). In addition, we believe that it will be indeed important to test whether the translocation of AGO2 and/or PACT into SGs impairs the various activities of Dicer and the RISC complex, for example, pre-miRNA processing.

The activity of specific miRNA species is involved in the stress response

miRNAs contribute in different contexts to modulation of the stress response, by adjusting the levels of key unfolded protein response (UPR) components. For example, miR-214 regulates ATF4 levels (Wang et al, 2013), and miR-30c-2* is upstream of Xbp1 (Byrd et al, 2012). In addition, maturation of a few miRNA species is downstream of IRE1, one of the three arms of the cellular stress response. IRE1, commonly known for its activity in splicing Xbp1 in the cytoplasm, terminates specific pre-miRNAs by preventing them from being further processed by Dicer into their mature forms (Upton et al, 2012). Therefore, miRNAs fine-tune the expression of components of the UPR signaling cascade and modulate cellular adaptation to stress, which is further reviewed in (Byrd & Brewer, 2013; Chitnis et al, 2013; Maurel & Chevet, 2013).

Additional influential reviews (Mendell & Olson, 2012 and Leung & Sharp, 2007, 2010) describe potential network architectures for the influence of miRNAs on stress signals: (i) miRNAs may dampen a stress signal if wired in a negative feedback loop or (ii) miRNAs may promote pathway activation via the inhibition of negative regulators within a positive-feedback loop. (iii) Finally, miRNAs may generate a threshold in responsiveness, because the relative levels of miRNAs and mRNA targets determine how much target protein is effectively produced (See Fig 4).

This last aspect of miRNA activity warrants further discussion. Long-lived miRNAs generate threshold for activation, which contributes to filtering transient or low-amplitude signals. Dynamic increase in the expression of a miRNA would contribute to a higher threshold and hence to tolerance toward specific stressor agents or to stress pre-conditioning. Examples for buffering may be observed in regulation of MICA and MICB, two stress-induced ligands that mark cells for destruction. The miR-17-92 family chronically represses MICA/MICB mRNAs levels, thereby filtering fluctuations in expression under normal conditions. However, when MICA/MICB transcription is induced at higher levels, to an extent that overcomes the threshold of miRNAs, cell destruction ensues (Stern-Ginossar et al, 2008). In another intriguing example, miRNAs encoded by herpes simplex virus 1 continuously repress viral proteins and provide the molecular basis of long-term latency in neurons. In this case, stress enables breakdown of the miRNA-based inhibitory mechanism and allows for reactivation of dormant viruses (Umbach et al, 2008).

miRNA activity and stress signaling in human disease

miRNA activity and stress signaling in animal models

Under favorable laboratory conditions, the loss of miRNA function infrequently exhibits dramatic phenotypes, unless aggravated by stress. Horvitz and co-workers have shown that many C. elegans miRNAs are dispensable under normal conditions and even the elimination of whole miRNA gene families was of surprisingly limited impact. However, genetic knockout of specific miRNAs renders the mutant animals incapable of coping with stress (Miska et al, 2007; Alvarez-Saavedra & Horvitz, 2010). This conclusion holds true also in mammals. For example, loss of miR-208a activity does not affect cardiovascular function, yet it abrogates stress-responsive cardiac remodeling (van Rooij et al, 2007). Likewise, nullification of miR-375, a miRNA highly expressed in the endocrine pancreas, exhibits mild impairments in glucose homeostasis, but these are aggravated by leptin-resistance obesity (Poy et al, 2009). These examples suggest that miRNAs will be particularly relevant to investigations of the response of fully developed tissues to stress (Leung & Sharp, 2010). In the same train of thought, it is plausible that miRNA insufficiency will be particularly evident in disease states.

Stress is a component of many adult-onset diseases

Cellular stress is often considered a vector of pathology. Aberrant protein folding and aggregation ignite UPR, which is evident in many chronic diseases including cardiovascular diseases (Minamino et al, 2010) and diabetes. Diabetes is a common metabolic disease, whereby insulin supply does not meet the body’s demands. The endocrine pancreas is under high demand for insulin synthesis in diabetes. The typical progressive reduction in beta cell mass observed in diabetes requires that the remaining beta cells increase...
insulin synthesis, which subjects them to increased UPR stress. Accordingly, modulation of the stress response is considered a potential therapeutic target in diabetes. For example, a chemical chaperone of unfolded proteins, sodium phenylbutyrate, was able to reduce UPR/ER stress and to restore glucose homeostasis in a mouse model of diabetes (Ozcan et al., 2006; Ozcan & Tabas, 2012).

Stress is evident also in brain diseases and particularly in neurodegeneration. Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease of the motor system (Al-Chalabi & Hardiman, 2013). Motor neurons in ALS are thought to agonize under stress (Atkin et al., 2008), and ER stress components including Perk (Wang et al., 2011), Gadd34 (Wang et al., 2014), and phosphorylation of eIF2a (Kim et al., 2014) were shown to modulate disease progression in a mouse model of ALS. Moreover, Salubrinal, an ER stress-protective agent, attenuates ALS manifestations and delayed progression in similar disease models (Saxena et al., 2009). Stress is plausibly playing comparable roles in other neurodegenerative states, including Alzheimer’s disease, where deposition of aggregated beta-amyloid triggers ER stress (Lee do et al., 2010).

RNA-binding proteins and stress granules in neurodegeneration
Accumulation of cytoplasmic granules is a patho-histological hallmark of several neurodegenerative diseases, including ALS. Mutations in the genes encoding for RNA-binding proteins TDP-43 and FUS were recently identified as causative in human ALS (Sreedharan et al., 2008; Kwiatkowski et al., 2009; Vance et al., 2009). These RNA-binding proteins are commonly found within SGs (Bosco et al., 2010; Parker et al., 2012; Daigle et al., 2013). TDP-43 is essential for proper SG assembly, and both TDP-43 and FUS interact with SG core components (McDonald et al., 2011; Aulas et al., 2012; Vance et al., 2013). Additionally, the mutated forms of TDP-43 and FUS both have the propensity to enhance aggregation (Bosco et al., 2010; Liu-Yesucevitz et al., 2010), and SGs containing TDP-43 or FUS tend to be more persistent, larger, and more abundant (Vance et al., 2013; Baron et al., 2013). Altogether, ALS-causing mutations in RNA-binding proteins contribute to the emergence of stress granules, which may aggravate other cues for SG formation in neurodegeneration. Importantly, TDP-43 and FUS are involved in miRNA processing. TDP-43 is a co-factor of both Drosha and Dicer, promoting the biogenesis of a subset of miRNAs (Buratti et al., 2010; Kawahara & Mieda-Sato, 2012; Li et al., 2013), and FUS stimulates biogenesis of a specific subset of miRNAs as well (Morlando et al., 2012). Therefore, these specific RNA-binding proteins provide a new intriguing link between miRNA bioprocessing, SGs and neurodegeneration.

Altered SG dynamics occur also in other neurodegenerative diseases. ATXN2 concentration impacts SG assembly by interaction with SG components PABP1 and Dead box helicase 6 (DDX6/RCK) and by regulating the translocation of FUS to the cytoplasm (Nonhoff et al., 2007; Farg et al., 2013). This may be relevant to the increased risk for ALS observed in ATXN2 intermediate-length polyglutamine expansions (Elden et al., 2010). SGs also play a role in Alzheimer’s disease (Vanderweyde et al., 2012), where SG components TIA-1 and tristetraprolin (TTP) bind phospho-tau. DDX6/RCK and ribosomal protein S6 were observed in degenerating granulovascular pyramidal neurons (Castellani et al., 2011). Altogether, the modulation of stress and SG formation plays a role in several neurodegenerative diseases, suggesting potential molecular commonalities for these conditions, regardless of the neuronal cell type involved or the particular clinical manifestations.

miRNAs in control of aging and age-related diseases
Aging is often characterized by the declined ability to cope with cellular stress. Several sources of internal cellular stress were suggested to impact longevity. Such insults include impaired mitochondrial activity, excessive production of ROS, DNA damage, and excessive accumulation of misfolded proteins (Finkel & Holbrook, 2000; Ishii et al., 2002; Gerstbrein et al., 2005; Heidler et al., 2009; Brown & Naidoo, 2012; Van Raamsdonk & Hekimi, 2012; Taylor & Dillin, 2013). miRNAs ensure developmental robustness and homeostasis (Hornstein & Shomron, 2006) and reinforce cellular programs also in the adult life (Li et al., 2009; Pelaez & Carthew, 2012; Cassidy et al., 2013). Therefore, dysregulation of miRNA function may contribute to aging by allowing the activation of aberrant pathways that are repressed by normal miRNA activity in younger individuals (Ibanez-Ventoso & Driscoll, 2009).

One of the most established examples in this emerging field focuses on miR-34, a specific miRNA family with conserved functions in control of aging and age-related diseases. miR-34 is up-regulated in aging nematodes (Kato et al., 2011), and mir-34 over-expression extends Drosophila life span and reduces the propensity to acquire age-related neurodegeneration (Liu et al., 2012). In human neurodegenerative diseases, both up- and down-regulation of miR-34 have been observed. miR-34 is down-regulated in human Parkinson’s disease brains (Minones-Moyano et al., 2011). In contrast, miR-34c is up-regulated in aging mice, in mouse models for Alzheimer’s disease, and in patients. Furthermore, miR-34c over-expression impairs memory, whereas targeting miR-34c rescues memory function in a mouse model for AD-linked amyloid pathology (Zovoillis et al., 2011). miR-34 is also up-regulated in plasma of patients of Huntington’s disease (Gaughwin et al., 2011) and in the organ of Corti in a mouse model of age-related hearing loss (Zhang et al., 2013). Altogether, it appears that miR-34 is involved in regulation of proper aging and of age-related brain diseases, suggesting potentially complex roles, which may include compensatory mechanisms.

miRNA activity per se is also critical in the C. elegans life cycle. Dysregulation of many miRNAs was observed in aging C. elegans with impact on longevity (Ibanez-Ventoso et al., 2006; Kato et al., 2011). A series of exciting studies on this topic from the laboratory of Frank Slack are reviewed in Smith-Vikos & Slack (2012) and Inukai & Slack (2013). One of the earliest works in this field showed that lin-4 and its target, lin-14, regulate the insulin growth factor (IGF)/DAF-16 pathway, which is a primary cascade for control of aging in nematodes (Boehm & Slack, 2005). Intriguingly, the expression of other miRNAs is up-regulated in aging animals, which may be a protective, compensatory response. For example, miR-71, miR-238, and miR-246 prolong life span and at least miR-71 functions via the IGF/DAF-16 (de Lencastre et al., 2010; Pincus et al., 2011; Bouillas & Horvitz, 2012).

In addition to the function of individual miRNA genes, a global decrease in miRNA abundance or activity has been observed in aging organisms and suggests that the whole miRNA regulatory network may play a role in aging and late-onset diseases (Ibanez-Ventoso et al., 2006; Drummond et al., 2011; ElSharawy et al., 2012; Imukai et al., 2012; Liu et al., 2012; Mori et al., 2012). In nematodes,
miRNA-binding proteins Argonaute-like 1 (alg-1), Dicer, Drosha, and DGCR8/Pasha regulate aging and control life span (Kato et al., 2011; Lehrbach et al., 2012; Mori et al., 2012). The activity of at least one of these miRNA-binding proteins, Dicer, decreases also in aging mammals; Dicer was found to be globally down-regulated in old mouse tissues in comparison with their younger adult counterparts (Nidavolalu et al., 2013).

In another study, Dicer activity was reduced in aging adipocytes of rodents and humans, noting concomitant reduction of miRNA expression (Mori et al., 2012). Likewise, Dicer activity is reduced in cerebro-microvascular endothelial cells of aged rats (Ungvari et al., 2013) and in age-related macular degeneration in humans (Kaneko et al., 2011; Tarallo et al., 2012), although the critical role of Dicer in this model was suggested to regulate ALU mobile elements.

Together, these observations suggest a link between age-related Dicer dysfunction and loss of robust cellular function. Reduction in Dicer levels lessens stress tolerance, whereas increased stress further inhibits Dicer activity (Lim et al., 2011; Mori et al., 2012). Because normal Dicer activity contributes to stress resistance, our proposed model suggests a vicious cycle, in which Dicer dysfunction and loss of robust cellular function. Reduction in miRNA regulation and various aspects of the cellular stress response are tied together. The data reviewed above suggest the presence of compensatory mechanisms, whereby miRNA functionality takes part in the physiological stress response, which are required for appropriate execution of the stress response and for proper cellular adaptation. However, stress signaling potentially alters the function of the miRNA-bioprocessing core components and leads to decompensated regulation. The consequences may include a potentially vicious cycle, whereby stress in the aging organism impairs miRNA processing, which in turn renders cells even more prone to stress.

Aging is characterized by progressive decline of robustness and stress resistance. miRNAs are used to ensure cellular robustness and homoeostasis (Hornstein & Shomron, 2006; Ibanez-Ventoso & Driscoll, 2009; Pelaez & Carthew, 2012; Cassidy et al., 2013). Alterations of miRNA expression can occur as a response to stress-related phenomena in a variety of diseases. However, currently, it is not clear whether the dysregulation of a single miRNA or a subset of miRNAs presents the cause or the consequence of an altered cellular phenotype. What pathways may modulate dysregulation of miRNAs in aging and disease? Many research efforts will be directed in coming years towards deciphering the role of miRNAs of various aspects of human disease and to uncovering the potential therapeutic activity of manipulating miRNA expression.

### Conclusion

miRNA regulation and various aspects of the cellular stress response are tied together. The data reviewed above suggest the presence of compensatory mechanisms, whereby miRNA functionality takes part in the physiological stress response, which are required for appropriate execution of the stress response and for proper cellular adaptation. However, stress signaling potentially alters the function of the miRNA-bioprocessing core components and leads to decompensated regulation. The consequences may include a potentially vicious cycle, whereby stress in the aging organism impairs miRNA processing, which in turn renders cells even more prone to stress.

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### Conflict of interest

The authors declare that they have no conflict of interest.

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