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REGULATION OF microRNAs DURING BIOTIC AND ABIOTIC STRESS

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Abstract

MicroRNAs (miRNAs) are short non-coding RNAs approximately 22 nucleotides play key roles in fundamental cellular processes, comprising how cells react to changes in environment or, stress. Stress is the state when cells deviate from the current situation due to sudden environmental changes or frequent fluctuations in environmental factors. Apart from the cellular concentration of miRNAs, the target gene repression level is also dependent on the concentration of mRNA target relative to the miRNA. From the previous studies it is seen that many aberrant expression of many miRNAs is induced by abiotic stressors so that miRNAs can be used as a new target for genetically improving plant tolerance to many stress. miRNAs respond to environmental stress mainly tissue and genotype-dependent manner. During abiotic stress, miRNAs function by regulating target genes within the miRNA-target gene network and by controlling signalling pathways and root development. In this review, we revisit the processing of microRNAs in animals and plants, history of miRNAs and condense recent findings in miRNA biogenesis and microRNAs involved in biotic and abiotic stress.

Keywords: microRNA, Stressors, Biotic, Abiotic, Xenobiotics

INTRODUCTION

MicroRNAs (miRNAs) are a class of small non-coding RNAs of 18-22 nucleotides in length that are conserved across species and they regulate gene expression at the post-transcriptional level (Wang et al., 2016). One of the crucial mechanisms of their action is the interaction of their "seed" sequences with 3′-end, or rarely with 5′-end, of mRNA transcribed from target genes, followed by mRNA degradation. The decrease in the amount of a specific mRNA is a key result of this molecular event. They are important regulatory molecules in many biological processes like embryogenesis, proliferation, differentiation, apoptosis and also have a role in the development of different diseases including cancer, diabetes, cardiovascular diseases, obesity, and viral infections (Chang and Mendell, 2007, Tang et al., 2008, Lanford et al., 2010). Over 60% of all mammalian mRNAs are predicted targets of miRNAs (Friedman et al., 2009) and miRNAs constitute a sizable class of regulators even outnumbering kinases and phosphatases, indicating their pervasive roles in the regulation of cellular processes.

Plant microRNAs are near perfect complementarity between miRNAs and their targets, whereas animal miRNAs are partially complementary to their targets (Millar and Waterhouse 2005; Axtell et al., 2011). Plant pre-miRNAs have larger and more variable stem- loop structures compared to animal microRNAs. Plant miRNAs act like siRNAs due to near-perfect complementarity with their target and specificity (Yang et al., 2007). Identified mature miRNAs such as 168 species including viruses, a filamentous brown alga (Ectocarpus siliculosus), a diatome (Phaeodactylum tricornutum), a soil-living amoeba (Dictyostelium discoideum), a green alga (Chlamydomonas reinhardtii), plants, and animals, have been deposited in the publicly available miRNA database (miRBase v18 release November 2011; http: / / www. mirbase.org) Kozomara and Griffiths-Jones 2011).. 4014 miRNAs (52 plant species) have been loaded in the mirbase since the discovery of plant miRNAs in 2002 (Park et al. 2002; Reinhart et al., 2002).

Previous studies have shown that miRNAs play a vital role in the gene regulatory networks, developmental processes and in stress responses (Jones-Rhoades et al., 2006; Sunkar et al., 2012). MicroRNAs play crucial roles in the regulation of siRNA biogenesis. Various stress responses which affect the microRNA expression profiles are such as salinity, drought, mineral- nutrient, mechanical, pathogen stress, etc (Liu et al., 2008;).

In this review, we revisit the processing of microRNAs in animals and plants, history of miRNAs and condense recent findings in miRNA biogenesis and microRNAs involved in biotic and abiotic stress in plants and animals.

HISTORY OF microRNA

miRNAs were discovered by Lee and colleagues 93 in the nematode *Caenorhabditis elegans* in 1993, *lin-4*, which was originally found in 1981 in *C. elegans* (Chalfie et al., 1981). These microRNAs functioned as small temporal RNAs (sRNAs) that regulate developmental transitions in *C. elegans* (Millar and Waterhouse 2005*)*. This unique mode of regulating gene expression was first believed to be a phenomenon exclusive to *C. elegans*. Later on, in 2000, 2 separate groups discovered that a small RNA, let-7, was essential for the development of a larval stage to adult in *C. elegans* (Slack et al., 2000). More notably, homologues of this gene were subsequently discovered in many other organisms, including humans. The unique discovery was that *lin-4* produced a pair of short RNA transcripts regulating the larval growth timing by translational repression of *lin-14,* by sequence complementarity between *lin-4* and the 3' untranslated region (3'UTR) of *lin-14* mRNA (Olsen and Ambros, 1999; Wightman and Ruvkun, 1993).

After the discovery of miR gene lin-4 in *C.elegans*, which is considered as the first miR gene, different miRNAs have been identified in both plants and animals. Functionally, plant miRNAs are involved in many fundamental biological processes (Palatnik et al., 2003), such as leaf polarity (Chen et al., 2004), floral identity (Palatnik et al., 2003) stress responses (Jones et al., 2004), and auxin responses.

PROCESSING OF microRNA

Processing of miRNAs has been extensively studied in recent years (Starega-Roslan, et al., 2011, Finnegan and Pasquinelli, 2013). miRNAs are transcribed by RNA Polymerase II together with the host gene or independently of the host gene. miRNAs primary transcripts are recognised by microprocessor complex that contains RNA- binding protein DGCR8 and RNase III Drosha. This complex cuts prior-miRNAs and produces a pre-miRNA of 60 nucleotides. This allows miRNA to interact with Exportin-5 and Ran GTPase for further sequestration into the cytoplasm. In the cytoplasm, this protein-RNA complex is recognized by RNase III Dicer that cuts pre-miRNA into a mature form of miRNA. Several defects in miRNA biogenesis have been examined by Hata and Kashima (2015) and some examples of changes in the activity of microprocessor Drosha. Adenosine deaminases can cause the changes in miRNA abundance and sequence during embryogenesis, as revealed in transgenic mouse embryos (Vesely et al., 2012). The presence of sequences such as AU/UA within particular miRNAs that destabilize their secondary structure is another mechanism. The percentage of AU or UA dinucleotide (in either the 5′–3′ or 3′–5′ orientation), but not the total percentage of A + U, strongly correlated with the half-life of selected miRNAs abundant in the brain (Sethi P and Lukiw, 2009)

The miRNAs are formed from their own genes located in between protein-coding genes or within protein-coding genes on the chromosomes (Lagos- Quintana et al., 2001; Wang and Blelloch 2009). For the biogenesis of plant miRNAs, several conserved protein families are required to generate functional mature miRNAs. Firstly the miRNA genes are transcribed into miRNA transcripts (pri-miRNA) by RNA polymerase II (Lee et al., 2004). These contain an imperfectly self-complementary region and are processed into stem-loop secondary structures (pre-miRNAs) including mature miRNAs in one arm of the secondary structures. RNase III enzyme Dicer like1 (DCL1) with the aid of double-stranded RNA (dsRNA) binding protein Hyponastic leaves1 (HYL1) and a C2H2 zinc finger protein Serrate (SE) cleaves the primer transcripts to hairpin-like miRNA precursors "pre-miRNAs" (Park et al., 2002; Reinhart et al., 2002) miRNA:miRNA* duplexes are formed in the nucleus and methylated to 2'-OH of the 3' –terminal nucleotide of each strand by the 3´-methyltransferase Hua enhancer1 (HEN1) Yang et al., 2006). This methylated end of miRNA/miRNA* duplex provides the biochemical requirement for the Dicer cleavage activity, which is a crucial step in miRNA biogenesis (Li et al., 2005). The methylated miRNAs/miRNAs* (pre-miRNAs) are transported from the nucleus into the cytoplasm by a protein known as Hasty (Hst) (Bollman, et al., 2003). On reaching the cytoplasm the miRNA duplex gets detached. The miRNA strand is selectively incorporated with RNA- induced silencing complex (RISC) and the other strand is degraded (Baumberger and Baulcombe 2005). Argonaute proteins 1 (AGO1) was also found to be one of the most important members of miRNA biogenesis in plants (Vaucheret et al., 2004). AGO proteins have two conserved RNA binding domains: an N-terminal PAZ domain that can bind to the 3-end of single-stranded RNAs, and a PIWI domain, which is responsible for the endonuclease activity of RISC (Cerutti et al., 2000). Finally, functional mature miRNA with AGO1 protein cleaves the target mRNAs or the translational repression of target mRNAs (Mi et al., 2008).

INFLUENCE OF HYPOXIA, HORMONES AND XENOBIOTICS ON miRNA EXPRESSION

The expressions of microRNA are affected by diverse types of hypoxia. Dysregulation of microRNA expression in microglia and CNS cells during chronic intermittent hypoxia were demonstrated by (Kiernan et al., 2016). MicroRNA expression profiles are observed in a tumour under the hypoxic condition.

Various physiological and pathological stimuli, such as steroid hormones can affect miRNA expression. miRNAs play a significant role in the resistance of breast cancer to hormonal therapy. A number of microRNAs were identified (miR-10a, miR-26, miR-30c, miR-126a, miR-210, miR-342, miR-519a), the expressions of which altered after tamoxifen treatment of patients with breast cancer. Estrogen-induced miRNAs are important for adrenomedullin balance – the key regulator of cardiac activity among women (Wetzel-Strong et al., 2016). miRNA expression can also be affected by corticosterone. The expressions of 26 miRNAs were changed under corticosterone-mediated

depression in rats, which can regulate closely related genes involved in the development, inflammation and depression (Dwivedi et al., 2015).

MicroRNAs can also serve as markers of toxicity of xenobiotics, which can be used for early diagnosis of cancer. Thus, it has been demonstrated that the treatment of embryonic fibroblasts with 2, 3, 7, 8-tetrachlordibenzo-p-dioxin or under the influence of ionizing radiation the expression of 5 miRNAs (miR- 29b, miR-31, miR-101a, miR-130a and miR-199a-5p), were altered (Huumonen et al., 2015). Aflatoxin B1, similar to benzo(a)pyrene, is a genotoxic carcinogen that can affect the profile of microRNA expression. Mechanisms of action of xenobiotics on microRNA expression can be mediated by nuclear receptors. For example, some microRNAs are expressed through AhR-dependent mechanism (Hu et al., 2013, Hecht et al., 2014). It has been shown that phenobarbital-mediated activation of constitutive androstane receptors (CAR) is accompanied by the decrease in miR-122 in liver (Kazantseva et al., 2015). Using sequencing techniques changes in the miRNA expression were detected in hematopoietic progenitor cells in C57BL/6 mice exposed to a prolonged 4-week treatment of benzene (Wei et al., 2015). The suppression of miRNA-451a or miRNA-486-5p is associated with the benzene-induced perturbation of erythroid cell differentiation a study revealed by Liang et al., 2017. miR-34a was observed to be involved in benzene-induced hematotoxicity by targeting Bcl-2 and could be regarded as a potential novel biomarker for benzene toxicity (Chen et al., 2016).

Many studies have been done regarding the miRNA regulation on drought tolerance in plants. MiR167, miR168, miR171, and miR396 were found to be drought stress-responsive miRNAs in Arabidopsis. The relative expressions of miR398 and miR408 are increased in *Medicago truncatula* during drought thereby inhibiting mRNA targets. miRNAs in barley such as miR156, miR166, miR171, and miR408, were differentially expressed on dehydration (Kantar et al., 2010). In poplar, the expression of miR102, miR156, miR162, miR167, and miR473 was upregulated under drought-influenced conditions. During salt stress, it was reported that several miRNA, such as miR396, miR168, miR167, miR165, miR319, miR159, miR394, miR156, miR393, miR171, miR158, and miR169, responded. miR 396 is another salt responsive plant miRNA targeting growth regulating factor (GRF) transcription factors (Chi et al., 2011). Also in poplar during salt stress, miR530, miR1445, miR1446, miR1447, and miR171 were down-regulated, whereas miR482.2 and miR1450 were up-regulated (Lu et al., 2008). During cold stress in rice, the members of miR171 are differentialy regulated (Lv et al., 2010). In *Arabidopsis*, miR165/166, miR169, miR172, miR393, miR396, miR397, miR402, and miR408 were expressed at higher extent whereas miR398 was expressed to a lesser extent in cold stress. In beans miR2118 was found to be up-regulated under cold stress (Sunkar and Zhu 2004; Zhou et al., 2008). Recently many miRNAs have been identified during abiotic stress in important crops or model plants under salinity, nutrient deficiency, heat, etc. However, this stress-regulated miRNA expression does not essentially confirm that the miRNA is involved in plant's adaptation to stress conditions. Differential expression of as many as 1062 miRNAs in 41 plant species under 35 different types of abiotic stress was observed.

In addition to abiotic factors, biotic factors such as bacteria, viruses, fungi, and insects also affect plant growth and productivity. Recently the roles of small RNA in disease resistance responses were reported (Navarro et al., 2006). Navarro et al. (2006) reported miR393 as responsive plant miRNA upon bacterial inoculation. The expression levels of miR160 and miR167 were found to be upregulated in the non-pathogenic inoculation, *Pseudomonas syringae* pv. tomato (Pst) DC3000 hrcC mutant. MiR398 was found to be expressed to a lesser extend upon oxidative stress treatment through bacterial pathogen infection by inoculating Pst avirulent strains to *Arabidopsis* plant (Jagadeeswaran et al., 2009). In wheat, a total of 125 putative wheat stress responsive long non-protein coding RNAs were identified during abiotic stress under fungal pathogen infection (Xin et al., 2008).

CONCLUSION

MiRNAs are considered to be key factors responsible for the specificity of post transcriptional regulation during growth, development and stress conditions in all organisms. In the present review, we have summarized the discovery, biogenesis of miRNAs and emphasised the role of particular

miRNAs and their targets involved in various stress responses. The significance of miRNAs in regulating growth, development regulation and responses to various external stress has been well recognized. MicroRNAs that are sensitive to xenobiotics and hormones could be regarded as a sensitive biomarker during toxicity induced by them.

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