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miRNA as a Potential Source for Combating Biotic and Abiotic Stress in Plants and Cancer Treatment in Humans

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Abstract

MicroRNA belongs to the class of endogenous non coding RNAs, they modify the expression of their target gene in both plants and animals. In this review, the potential of miRNAs is discussed to help the plants resist biotic and abiotic stress. We will also bring insight the application of miRNAs a potential tool to diagnose various level of cancer metastasis and an effective method for cancer treatment. These miRNAs are target specific and are likely to regulate responses like plant-pathogen interaction, signaling pathways, metabolism, etc. in the plants. While their uneven expression and target regulation during the cancer makes them an effective source to work as biomarker. There is research where miRNAs were used along with nanoparticles to treat cancer and were found to be useful. This study will provide us with some evidence to demonstrate the molecular role of miRNA in plant to response against various stresses and differential expression of miRNA with their target gene regulation during cancer metastasis.

Keywords: MicroRNA; Cancer; Biotic stress; Abiotic stress

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Introduction

miRNA is a small non-coding RNA molecule found in abundance in the cell of plants, animal and in some viruses. They play a vital role in gene expression by post-transcriptional modification of mRNA molecule. They have the capability to silence the mRNA molecules by either cleaving it into two pieces or shortening poly(A) tail to reduce its stability. They might even reduce the efficiency of mRNA translation into protein [1]. miRNA show resemblance to siRNAs in their RNAi pathway, whereas they are structurally different from siRNAs on accounts of their RNA transcript region that fold back and forms short hairpin like structure [2]. It is estimated from the resent studies that a human genome can code over 600 miRNAs. It is found that many miRNAs remained evolutionarily conserved in mammals, which signifies their importance in biological functions [3].

First miRNA was discovered in 1993 by Victor Ambros in *Caenorhabditis elegans*. It was named as lin-4 which regulated lin-14 gene protein level. This lin-4 RNA binds to partial antisense sequence on 30-UTR and suppresses the translation of lin-4 [4] later on this lin-4 became an established member of miRNA family and many studies are being carried out the regulatory potential of these sRNA. Researches are conducted to find out the role of miRNA towards the stress response and different development pathways found in plants and animals.

Evidence of miRNA was first found in *Arabidopsis* plants which was subjected to stress. With the help of silicon-based analysis miRNA and their target gene were studied for the first time [5]. These miRNAs were only reported in the samples drawn from the stressed plants [6,7]. There were sixteen miRNAs discovered amongst which eight belonged to the conserved region in rice. Therefore, we can say that miRNAs in plants belongs to the endogenous non-coding sRNAs required for the growth, development and survivability of the plant.

Researchers have found that sRNAs can target chromatin and transcripts to keep genome and transcriptome under regulation. According to studies and through the use of high-throughput sequencing a whole new dimension of small RNAs in eukaryotic

cells is observed. Based on their distinctive character they are classified into three classes (based on biogenesis and Argonaute protein): microRNAs (miRNAs), endogenous small interfering RNAs (endo-siRNAs or esiRNAs) and Piwi-interacting RNAs (piRNAs) [8].

Literature Review

Biogenesis of miRNA in plants

When we talk about the biogenesis of miRNA in plants initiates with the conversion of non-coding region into Pri-miRNA. This Pri-miRNA is then processed by DICER-LIKE 1 to produce Pre-miRNA inside the nucleus. HYPONASTIC LEAVES1 and SERRATE interact with DCL1 in D-bodies which helps in the conversion of pri-to-premiRNA [9,10]. miRNA–miRNA* duplex is formed by DCL1 as the miRNA is unstable. Later on, HUA ENHANCER 1 (HEN1) to methylate small RNAs on the 30 terminals to protect against uridylation and degradation by the SDN (type of exonucleases) [11,12]. After being modified they are exported to the cytoplasm by HASTY where Helicase enzyme processes it in a mature miRNA [13]. Antisense strand of miRNA that gets associated with RNA-induced silencing complex (RISC) while the sense strand is degenerated [14]. There is a complex formed by this single strand miRNA with AGO-1 protein so the miRNA can bind to the complementary mRNA target. The destiny of this mRNA is decided by the degree of complimentary sequence. If the sequence is nearly complimentary mRNA is completely degraded while partial complimentary sequence can lead to the repression of the protein transcription level [14].

Biogenesis of miRNA in animals

Just like in plants, miRNAs in animals also are transcribed directly from the DNA template in nucleus as long variable length hairpin Pri-miRNA by RNA polymerase II. Drosha and the RNA binding protein DGCR8 processes Pri-miRNA in the nucleus to form 70- to 120-nucleotide long Pre-miRNA. This Pre-miRNA is then exported to cytoplasm by exportin 5, where Dicer removes the loop region of Pre-miRNA and an 18- to 23-nucleotide-long mature miRNA molecule is formed. Dicer-miRNA complex enters into RISC that contains AGO2, protein kinase RNA activator (PACT), trinucleotide repeat- containing gene 6A (TNRC6A), and other RNA binding proteins (E) through transactivation response RNA binding protein (TRBP). Once the miRNA is incorporated in RISC, “passenger” strand is degraded whereas the “guide” strand does not. Now this miRNA will be guided to the target mRNA molecule and its fate will be decided on the degree of the complimentary sequence between them. There is evidence that shows that transcripts bound by miRNA-incorporated Ago2 are channeled into structures called P-bodies, resulting in translational repression (Loosely adapted and redrawn from Bhaskaran M et al. [15]). (**Figure 1).**

In this review, we owe to discuss the governing role of miRNA in combating Biotic as well as Abiotic stress in plants to facilitate the further research scope in the usage of miRNA in improving the quality and quantity of crops by allowing them to withstand abiotic stresses like salinity, high temperature etc. as well as biotic stresses like fungal attack, bacterial infections etc by manipulation

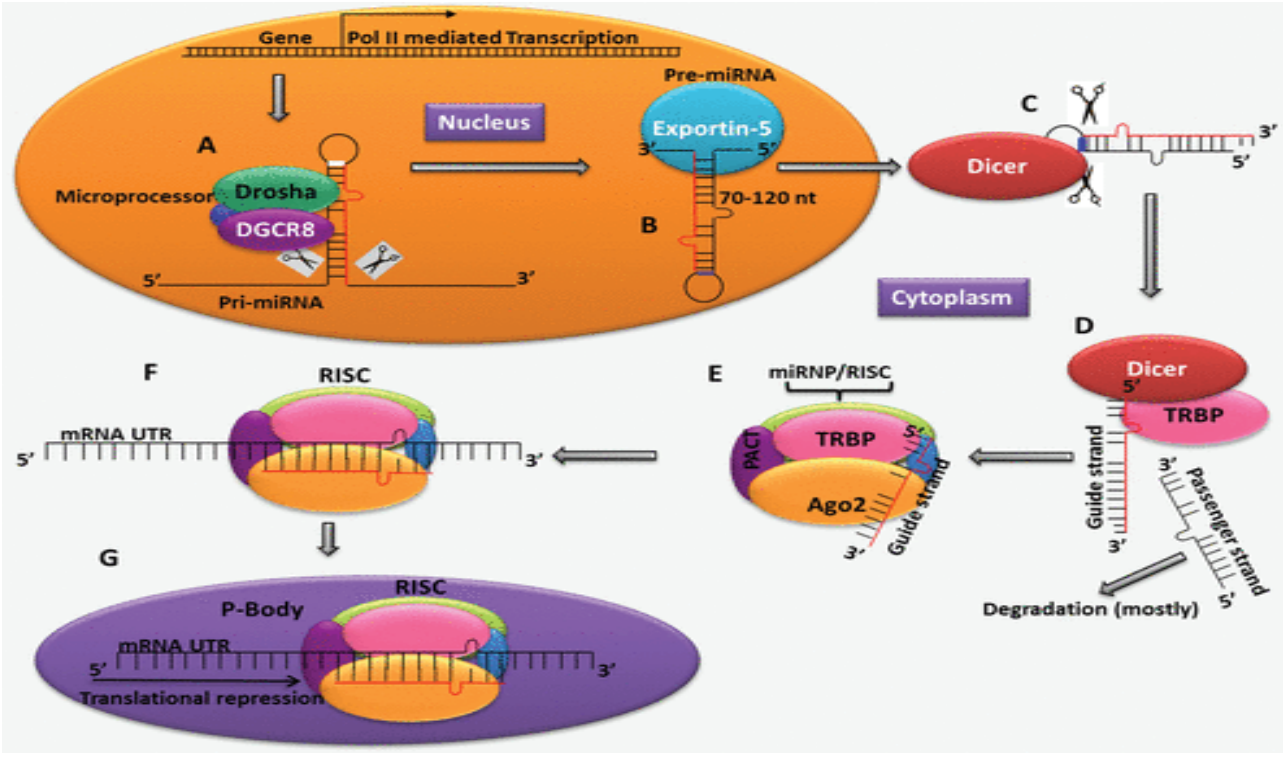

Figure 1 Canonical microRNA (miRNA) biogenesis pathway [15].

of miRNA/siRNA- guided gene regulation. Here, we are even going to talk about the miRNA as an important tool for the diagnosis of various human cancers with their differential expression patterns and Usage of miRNA as a potent tool to suppress the metastasis of cancer in humans.

Role of miRNAs in plant stress responses

There is exponential increase in the population of the world which lead to an ever-increasing demand of food for growing population. Plants are highly sessile and are being exposed to various stresses in the environment which decreases the estimate production of crops along with decrease in their quality. There is a requirement for plants which are tolerant towards both biotic and abiotic stress condition to meet the nutrition requirement of the world. One possible solution to this problem is the use of RNA interference or artificially crafted miRNA. We clearly know the functions of miRNAs in animal cells, whereas the role of miRNAs in plant stress responses is still not clear. In a study carried out on *A. thaliana* seedling which was subjected to abiotic stress showed expression of several miRNAs in response towards environmental stress [16].

miRNAs and plant biotic stresses

Plants are faced with numerous biotic stresses (such as bacteria, virus, fungus, insects and nematodes) and adverse environmental conditions. They cause vascular wilts, stunting, chlorosis, lesions, leaf spots and cankers among other symptoms, and can infect different parts of the plant [17]. They respond to these stresses through several morphological, biochemical, and molecular mechanisms and evidence suggests that there are interactions among their respective signaling pathways [18]. These parasites are getting mutated through some unknown pathways and become resistant to various viricides, fungicides, insecticides, pesticides. This is becoming an ultimate reason for loss of crop yield all across the world and makes is necessary to find a possible solution for it [19].

In terms to tackle biotic stresses, plants have developed an effective immune system which gives them advantage over pathogens. The first line of defense in plants is passive. We all are familiar with physical barriers such as waxes, thick cuticles and specialized trichomes that are possessed by plants to prevent insects or pathogens from settling into the plant [4]. Basal defense and resistance (R) gene mediated resistance are the two well defined defense response carried out by the plants under pathogen stress. Basal defense marks the first line of defense which is consists of a set of defined receptors referred to as pattern recognition receptors (PRRs) that recognize conserved microbe associated molecular patterns (MAMPs), also called pathogen associated molecular patterns (PAMP) [20,21].

We have also observed, when a plant is subjected to biotic stress and a damage is done by the parasite it induces the expression of miRNA to inhibit the effects of biotic stress by down regulating their own self, to regulate resistant genes negatively. Discovery of small interfering RNAs (siRNAs) and micro RNAs (miRNAs) and their potential to regulate abiotic and biotic stress responses made them an important tool for being used in agriculture [19,22]. An extensive research work is carried out to find a solution towards this biotic stress amongst which one of the most prominent one is miRNA. miRNAs have been already identified in tomatoes subjected to biotic stress with the help of high throughput sequencing techniques [23].

These sRNAs have ability to move across plasmodesmata which is very essential for host response to disease and can be used to develop a remediation to reduce the chances of infection. They can easily transfer from cell to cell, tissue to tissue, and even shuttle one species to different species. AS sRNAs are short in length they are proved to be beneficial in regulating plant development and immunity [24].

miRNA is target specific and their regulatory functions can be used to provide resistance towards viral attack through cleavage of mRNA, translation inhibition, and methylation. miRNA is already implicated in suppressing cucumber mosaic virus in transgenic tobacco plant. Turnip yellow mosaic virus and HC- proof turnip mosaic virus was also found to get suppressed in *Arabidopsis thaliana* introduced with miR159 [25,26]. There are studies which gives us evidence that virus have the capability to alter the expression of miRNA in the host. There was a study carried out on sweet orange plants which were infected by two different strains citrus psoriasis virus which showed different symptomatology and changes the accumulation of miRNA i.e., miRNA156, miR167 and miR171. There expression was three-fold decreased in the samples of infected plants. This decrease in this miRNA was due to the hindrance in precursors of these miRNA i.e., pre-miR156 and pre-miR171 [27].

According to a recent study on grape vein which were infect by virus lead to the discovery of a new Grapevine vein clearing virus. Samples were tested for the expression of miRNA and it was found that 54 new miRNAs were identified amongst which 6 miRNAs (MIR17, 18, 19, 20, 21, and 22) were exclusively present only in the infected sample derived from the plants. It was found that VITIS-MIR18 was gene which coded for a protein that acts as a transcription factor responsible for development of plant and induces stress responses. Other miRNA which was induced due to viral attack i.e., miRNA168 and miRNA3623 were responsible for defense against the viral attack. Whereas, miRNA319 and miRNA395 were involved in metabolism. miRNA396 was involved in cell division [28].

Since, the first regulatory evidence of miRNA in the leaves of plant *Arabidopsis thaliana* infected by bacteria *Pseudomonas syringae pv. tomato (Pst) DC3000* [29] now there are many miRNAs induced due to the bacterial attack studied in *A. thaliana.* There is research which showed the transcription of mainly miR393a (auxin repressor) which is a negative regulator of plant defense. miRNA393a upregulated miR393, miR319, miR159, miR160, miR165/166, and miR167 and whereas downregulation of miR390, miR398, and miR408 observed. This clearly demonstrate that in *A. thaliana* plant resistance towards bacterial pathogen *P. syringae* was provided by miRNA393a [30]. *P. syringae*in terms have developed different protein (bacterial flagellin-derived peptide) to counter the regulation of miRNA393a. The mode of

action of bacterial flagellin-derived peptide against the miRNA393 is to negatively regulate mRNA for F-box auxin receptors transport inhibitor response 1 (TIR1), AFB2, and AFB3. While we talk about the transgenic species of plants there is an overexpression of miRNA393 which provides resistance to the plants towards the pathogen bacteria [31]. Mutated species of *A. thaliana* lacking miRNA were able to restore to their normal growth under the infection of non- pathogenic strains of bacteria [24].

miRNA plays a significant the role in providing basal defense to plants. Presence of miRNAs was also noted in the nitrogen fixing symbiotic bacteria growing in association with the roots of legume plants. miRNA was found to be associated with the regulation of their gene expression with regards to nitrogen fixation in those bacteria. In *Bradyrhizobium japonicum,* miR2606b and miR4416 regulates the expression of Mannosyl-oligosaccharide 1, 2-alpha-mannosidase and rhizobium-induced peroxidase 1 (RIP1)-like peroxidase [32]. Further the regulation of abscisic acid signaling pathway was under the control of miRNA159. While miRNA319 has control to regulate Jasmonic acid (JA) signaling cascade. Induced expression of miR2911 and miR1030 in plants like *X. axonopodis, Populus euphratica* and *Physcomithrella patens* is essential for host-pathogen interaction and also provides resistance towards bacterial infection [33]. It was found that when *Botryosphaeria dothidea* infected *Malus hupehensis*, miR168a provide the plant with resistance towards this pathogen [34]. In plants like cassava, miR395, miR397, miR398, miR408, miR482 and miR535 are down-regulated and the corresponding target genes are accumulated as an ETI response [35,36].

miR408 found in wheat cultivar is a negative regulator of plantacyanins and laccase [37,7]. Even though the exact role of plantacyanins in plants is mysterious; however, they are supposed to be involved in stress responses cell-to-cell signaling and lignin production [38,39]. Similarly, laccasesin plants is also associated with regulation of different task i.e., lignin synthesis, wound healing, iron, acquirement, stress response, cell wall structure maintenance and veracity [41,42]. Therefore, it can be said that after 2 day from inoculation (DAI) and 10 DAI, miR408 regulation in wheat cultivars susceptible and resistant to *Puccinia graminis f. sp. Tritici* [43] might result in plantacyanins and laccase- causes changes in lignin biosynthesis and HR response. miR2118 also shows the similar effect on targets TIR-NBS-LRR Verticillium-dahliae-infected Gossypium hirsutam [44]. Same as the above-mentioned miRNA, pbe-SR23 and pbe-SR3 in Populous targets TIR-LRR after Dothiorella gregaria attack [45]. Osa-miR7695 overexpression resulted in resistance to blast fungus. Os-miR7695-mediated negative regulation of natural resistance-associated macrophage protein 6 (OsNramp6) illustrated a novel regulatory network, integrating miRNA function and mRNA processing in plant immunity [46].

miRNAs and plant Abiotic stresses

Apart from that of biotic stresses, it was scientifically proven that the abiotic stresses also play a significant role in the growth of the plant. Due to the fluctuation in the environmental condition, there is a tremendous loss of agricultural crops every year [47,50]. When we talk about temperature, it is an important factor for the growth of plants i.e., maximum and minimum temperature of the day and also the average temperature effects the productivity of the crops [48,49]. A study on *Triticum aestivum L* showed that there is no production of fruits and abortion of formed grain in wheat during the frost period while the period of excess heat reduces the number of grains [51], this shows that climate change will lead to loss in productivity of the trend crops like pearl millet. [52-54].

When *Gossypium hirsutum* subjected to different range of temperature 319 known miRNAs and 800 novel miRNAs were identified, and 168 miRNAs were differentially expressed between different treatments. By analyzing the degradome sequencing respective targets of these miRNA were identified. On further studying it was found that they are involved in response to hormone stimulus, oxidation- reduction reaction, photosynthesis, plant–pathogen interaction and plant hormone signal transduction pathways [55] **(Figure 2).**

In *A. thaliana* Abiotic stress leads to the induction of miR169 and mi398 which were negatively regulated by virus in the Grapevine [32]. On performing miRNA microarray assay in maize, it was found that 98 miRNAs were expressed amongst which 27 miRNA showed alteration in expression during salt stress. 18 miRNAs were exclusively produced during salt encounter while 25 showed delay in their regulation pattern [56] miR395 and miR399 are up-regulated during sulphate and phosphate (Pi) deficiency, miR395 is responsible for sulphate assimilation by regulating the expression of ATP sulphurylase (APS) and a sulphate transporter (AtSULTR2;1). While miR399 is either overexpressed or their expression pattern changes during P_i toxicity; this increases the retention of Pi in old leaves and enhances root to shoot translocation of Pi. This suggests that the miR399 mediates the regulation of UBC24 expression is critical in Pi homeostasis [56].

Role of miRNA in cancer diagnosis and treatment

Since long we have known that cancer is a disease caused by uncontrollable cell division and spreads to nearby tissues, which

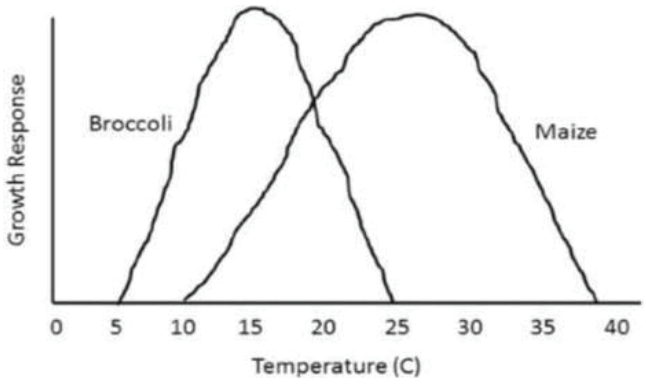

Figure 2 Broccoli (*Brassica oleracea var. italica*) growth response to temperature started from 5°C and retired at 25°C while that of maize (*Zea mays L.)* started from approximately 10°C and retired at approximately at 40°C.

is possibly due to specific changes on different locations on DNA (i.e., genes). With the advancement techniques it was found that miRNAs were some or the other way related to that of the cancer metastasis. For example, it was observed that a group of 6 miRNAs (miR-30c-1*, miR- 616*, miR-146b-3p, miR-566, miR-550) were significantly increased in patients suffering from adenocarcinoma (ADC) cancer. miR-106a and miR-21 were reported as independent prognostic miRNAs in Cholangiocarcinoma (CCA) [57].

Studies have also demonstrated overexpression of miR-335 and miR-543 reduces the expression of eNOS (nitric oxide synthase) in endothelial cell during primary prostate cancer while higher expression during bone metastasis. This suggests that different expression patterns of miR-335 and miR-543 are associated with prostate cancer and bone metastasis. Therefore, they can be used as a biomarker to identify different stage of cancer progression in human prostate cancer and give a predication regarding bone metastasis [58]. In mantle cell lymphoma, multiple myeloma and prostate cancer loss of miR-15a and miR-16-1 in CLL and 13q14 strongly supports that these two miRNAs acts a tumour suppressors as they reduce the amount of BCL2 which is important for the survival of the cancer cells [59]. miRNAs like let-7, miR-21, miR-22, miR-34, miR-101, miR-146a, and miR-200 are found to regulate oncogenic signaling pathways which mediates the characteristics of CSC. These miRNAs can serve a major role in therapeutic approach through which it was also stated that polyphenol compound, flavonoid compounds and vitamin D can have an inhibitory response towards growth of tumour cells [60].

Now-a-days Ex-miRNA is used to identify and understand subtypes of tumours. It can also indicate the severity of a tumour and its progression therefore it can be used to take discussion regarding to the clinical treatment to meet the need of the patient to be treated [61]. It was observed in cell line that tumour suppressor ex-miRNAs was released through exosomes. Tumour cell has the ability to reduce the intracellular concentration of this suppressor miRNA to increase oncogenesis. For example, Rab27 was knockdown in bladder cancer and causes reduction in exosomal export of tumour suppressor miR- 23b [62].

A study was carried out to check the impact of miRNA on the lung cancer and it was found that when GC4- targeted nanoparticle co-formulated with miR-34a in a mouse showed significant inhibition in metastasis nodules. In untreated control only 20% decrease in tumour load was quantified whereas 30 to 50% of the tumour load was reduced in the model treated with miR-34a. This indicates the therapeutic potential of siRNAs and miR-34a when delivered with nanoparticles [63]. When we talk about cancer it is consider as heterogenic disease which might involve more than one gene so targeting a set of oncogenes can have a therapeutic result. miRNA can target stromal cells and fibroblast which can promote tumour progression. Locked nucleic acid- antimir-122 is the first novel miRNA therapeutic strategy to successfully enter into clinical trial phase II for the treatment of hepatitis C virus (HCV) infection. miRNA-126 targeting VEGF and EGFL7 are used to get predictive knowledge towards the anti-angiogenic treatment [64,65].

Discussion and Conclusion

Through this study we conclude that miRNA has a potential to be used as biomarker for the detection of cancer and also it can be used as an effective major to eradicate the cancer metastasis. Further miRNA biogenesis pathway is widely studied in both plants and animals therefore it can be manipulated using artificial miRNA technology, its conserved nature can be exploited to serve as a potential tool for gene silencing in plants and develop resistance against potential plant pathogen. Although miRNA expression patterns are partially described in most cell types under normal conditions, aberrant expression of some miRNAs has been identified in various human diseases, implying that miRNAs can be beneficial as biomarkers for disease occurrence and as a possible target of treatment. It has been reported that miRNA expression in tumour is up or down-regulated compared with normal tissue confirming their complex dual action either as oncogene (oncomir) or tumour suppressor gene. Recently an amazing finding suggested that miRNAs are present in exosomes and these exosomal miRNAs (ex- miRNAs) can be functionally sent to target cells. In this review, we sum up latest advances in the exploration of ex-miRNAs in cancer. We also reviewed the possible clinical utilizations of ex-miRNAs in cancer, eg. as diagnostic markers and therapeutic targets.

Conflict of Interest

Authors declare no conflict of interest.

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