

## CIRCULAR RNA IN PLANT STRESS RESPONSES

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Article Received on 21/03/2022

Article Revised on 11/04/2022

Article Accepted on 01/05/2022

## ABSTRACT

CircRNAs are recently discovered non-coding RNA molecules, play significant role in diverse biological processes. Extensive research has uncovered its impact on animal system especially in several human diseases. However, their role in plants, particularly role in response to adverse environmental conditions are less explored. Here, we have discussed the differentially expressed circRNAs identified in several plant genomes in response to biotic and abiotic stresses and also their potential to predict phenotypical properties.

**KEYWORDS:** Non-coding RNA; stress; Expression; Signal transduction.

## INTRODUCTION

The existence of non-coding RNAs (ncRNAs) has been established since the inception of molecular biology.<sup>[1,2]</sup> The specifics of ncRNAs have, however, remained largely obscure in the shadows of coding RNA for several years due to the limitations of molecular techniques. Recent advancement in next-generation sequencing technology has led to the rapid characterization of ncRNAs and has significantly expanded our knowledge about their prevalence in the transcriptome.<sup>[3]</sup> Researchers have shown evidence regarding the regulatory, structural, and functional aspects of so-called Junk DNAs (ncRNAs) and gave rise to a new area of research.<sup>[4,5]</sup> In general, there are two types of ncRNAs, namely housekeeping ncRNA and regulatory ncRNA. Housekeeping ncRNAs are ubiquitous, abundant, constitutive, and perform essential functions.<sup>[6]</sup> These include ribosomal RNAs (rRNAs), transfer RNAs (tRNAs), small nuclear RNAs (snRNAs), and small nucleolar RNAs (snoRNAs).<sup>[7]</sup> Regulatory ncRNAs are divided into two classes, depending on the length, *i.e.* small non-coding RNA (sncRNA, 18-30nt; miRNA, siRNA, and phasiRNA) and long non-coding RNA (lncRNA, < 200 nt; lincRNA, incRNA and NATs).<sup>[8]</sup> Above mentioned lncRNAs are linear in confirmation, but in 1990s a new endogenously derived lncRNA was discovered known as circular RNA (CircRNA).<sup>[9]</sup> Previously, due to the limitations of conventional RNA analysis, they were considered as an artifact of aberrant RNA splicing. In the recent past, the advancement of sequencing technologies has gathered a substantial understanding of circRNAs.<sup>[10]</sup> CircRNAs are covalently closed, formed by 3'-5' head to tail ligation, therefore lacks 5'-3' polarity and polyadenylated tail.<sup>[11]</sup>

This mechanism confers resistance against RNAaseR (exoribonuclease) and is, therefore, more stable than linear RNA.<sup>[12]</sup> CircRNA may be exonic, intronic, and intergenic depending on its origin from genomic location.<sup>[13]</sup> CircRNAs from introns are retained in the nucleus, while those from exons tend to relocate to the cytoplasm.<sup>[14]</sup> Alternative circularization, in addition to backsplicing, results in a large number of circRNA isoforms that are generated from the same parental gene.<sup>[15]</sup> Intron lariat, which escapes debranching or intron precursors formed during exon skipping, also produces CircRNA.<sup>[16]</sup>

Studies on circRNA in the animal system have been performed extensively though it is still in its infancy in plants.<sup>[17,18]</sup> Variation in the plant and animal circRNA has been reported on account of certain features like the presence of the large number of reverse complementary and repetitive sequences in the flanking introns in animal's circRNA as compared to plant.<sup>[19]</sup> In circularization, these sequences play an important role, indicating different mechanisms prevailing in the animal and plant system with respect to circRNA biogenesis.<sup>[20]</sup> In animals, it has been documented that circRNA acts as a miRNA sponge and controls the expression of its target genes.<sup>[21]</sup> However, circRNA's ability as a miRNA sponge has not been exhaustively or practically proved in plants.<sup>[22]</sup> Despite the differences in circRNA in animals and plants, certain characteristics such as pre-mRNA backsplicing reaction, RNA polymerase II-mediated circRNA synthesis are preserved in both systems.<sup>[23,24]</sup>

Controlled and constitutively synthesized regulatory ncRNAs modulate gene expression at the transcription

and post-transcriptional level.<sup>[25]</sup> Recently, several reports confirmed their role in response to stress.<sup>[26,27]</sup> CircRNA expression varies between cells, tissues and depends on the stage of development.<sup>[28]</sup> Regulation of gene expression is considered the most prominent feature of circRNA.<sup>[29,30]</sup> Advances in transcriptome sequencing along with bioinformatic pipelines have shed light on how the complex circRNA-miRNA-mRNA network controls gene expression and development in plants.<sup>[31]</sup> The increased expression of certain circRNAs in plants (*Arabidopsis*, *Triticum*, *Solanum*, etc.) in response to biotic and abiotic stress was subsequently reported by several researchers.<sup>[22,32-34]</sup> Here, we addressed the function of circRNA in plants, particularly in response to stressful conditions. Besides, their functional role has also been demonstrated in biological processes and related biosynthetic pathways.

### CircRNA in plants:

Based on a genome-wide study first report on plant circRNAs was given by Ye et al 2015, where they identified circRNAs in two model plants namely *O. sativa* and *A. thaliana*.<sup>[35]</sup> Following which a few other genomes were analyzed for the identification of potential circRNAs (reviewed by.<sup>[24]</sup>) However, only a few of these circRNAs were experimentally validated in plant

systems. By the process of alternative circularization, a single circRNA can have a few different isoforms.<sup>[20]</sup> In other words, a single gene has the potential to encode different circRNAs, validated in the rice genome by RT-PCR.<sup>[35]</sup> Therefore, in near future, it is expected to get more circRNAs with the progress in sequencing techniques and advanced bioinformatic pipelines. Recently, a few bioinformatic tools (reviewed by.<sup>[36]</sup>) plant circRNA databases were released however, due to the high false discovery rate most of these prevailing tools are unsuitable for plant circRNA research.

### CircRNA in stress:

Being sessile organisms, plants are under the influence of unfavorable environmental conditions called biotic (attack by various pathogens viral, bacterial, fungal, nematodes, and other insects) and abiotic stresses (drought, salinity, chill, heat, low mineral/element content, metal toxicity, etc)<sup>[37]</sup> (Fig 1). Stress conditions have a devastating effect on the overall yield of crops of agronomical importance and have become a global challenge.<sup>[38]</sup> Plants employ a multitude of defense strategies to deal with numerous environmental factors [39]. Emerging reports suggest that circRNA in plant growth and development under stressful conditions plays a significant regulatory function.<sup>[19]</sup>

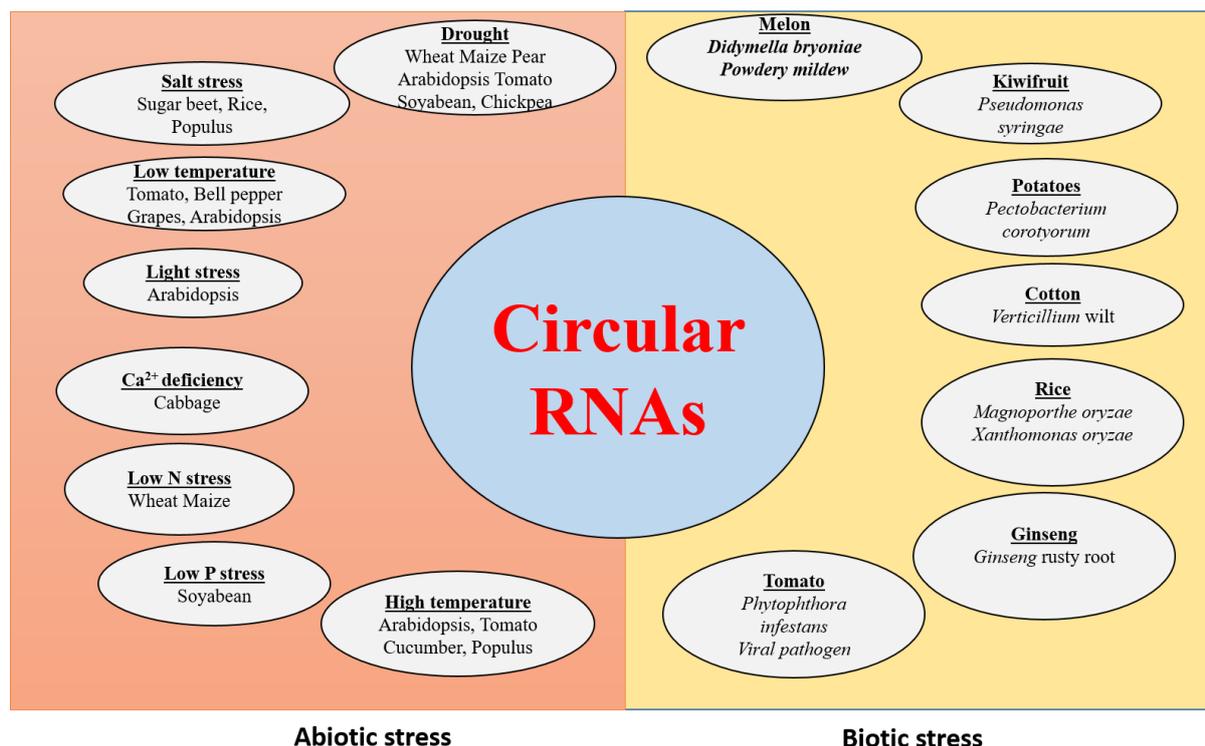


Figure 1: Identified circRNAs in plants in response to different Biotic and Abiotic stresses.

Drought is one of the main environmental challenges that affect the staple grains and fruits.<sup>[40]</sup> In wheat, maize, Arabidopsis, tomato, soybean, *Pyrus betulifolia*, and chickpea, the function of circRNAs in drought stress response was investigated.<sup>[19,33,41-43]</sup> 62 circRNAs were found in wheat that were differentially expressed in

seedlings stressed by dehydration.<sup>[33]</sup> Functional annotations of the mRNAs targeted by these circRNAs confirmed their involvement in the dehydration-responsive process. A substantial number of differentially expressed circRNAs were reported in maize, arabidopsis, chickpea, and soybean in response to

drought.<sup>[44]</sup> All the target genes show their role in species-specific pathways like hormone signal transduction, response to stress, response to auxin, and transcription factor activity.<sup>[45]</sup> The potential role of circRNAs in response to drought (4 circRNAs), heat (7 circRNAs), and multiple stresses (9 circRNAs) were also deciphered in tomato.<sup>[42]</sup> The main pathways regulated by these differentially expressed circRNAs were photosynthesis, starch and sucrose metabolism, RNA transport, RNA degradation, spliceosome, ribosome, etc.<sup>[42]</sup> Temperature also modulates the expression of circRNAs in plants.<sup>[46,47]</sup> Different studies have established the role of circRNA in different crops in response to cold stress.<sup>[22,48]</sup> For example, Zuo et al. (2016) reported chilling responsive differential expression of 163 circRNAs in tomato.<sup>[49]</sup> Plant growth and production involve numerous temperature-sensitive biochemical reactions.<sup>[50]</sup> Functional annotation of the targeted genes confirmed their participation in the chilling process, such as redox reaction-based enzymes, heat and cold shock proteins, energy-related metabolism, jasmonic acid, abscisic acid metabolism, low-temperature protein family, etc.<sup>[49]</sup> Chilling injury in bell pepper fruit revealed the differential expression of 36 circRNAs that play a role in signaling, cell communication, cellular process control, primary metabolic process regulation, temperature stimulation, etc.<sup>[51]</sup> 475 differentially expressed circRNAs were also reported in grape leaves under cold stress.<sup>[48]</sup> Gao et al. (2019) showed the overexpression of Vv-circATS1 (circRNA) in Arabidopsis which enhances the plants tolerance towards cold.<sup>[48]</sup> The correlations between circRNAs and their targets confirms the promising role of circRNAs against abiotic stress conditions.

In addition to cold stress, circular RNA also showed differential expression in high temperature-induced stress conditions. Several heat stress-specific circRNAs were identified in Arabidopsis and tomato.<sup>[34,52]</sup> CircRNA mediated ceRNA (Competing endogenous RNA) network study reveals that circRNA might influence the expression of genes that participate in response to stress and phytohormone signaling pathway.<sup>[34]</sup> The parental gene of these identified circRNAs were involved in metabolic, catalytic, and cellular activities.<sup>[53]</sup> Similarly, circRNA were reported in cucumber that targets hormone signal transduction pathway in response to high temperature stress via interacting with miR9748.<sup>[54]</sup> The function of Circ\_0003418 has also been elucidated in *Populus tomentosa* as a negative regulator to heat tolerance by regulating ubiquitin-mediated protein modification pathway.<sup>[55]</sup> Plant regulates its physiological adaptability under the conditions of light-related stress. Yang et al. (2020) identified 1650 light-responsive circRNA in lettuce and its regulatory effect on photoreactivity.<sup>[56]</sup> Light stress-specific circRNAs were also identified in the leaves of *Arabidopsis*.<sup>[35]</sup> In the same study, circRNAs under phosphate deficiency were also discussed in rice. A total of 27 circRNA were

identified in rice including 6 upregulated and 21 downregulated.<sup>[35]</sup>

Similarly, the role of circRNAs in response to salt stress was studied in rice<sup>[57]</sup> Zhou et al. 2021), sugar beet.<sup>[58]</sup> *Populus euphratica*.<sup>[59]</sup> 93 differentially expressed circRNAs were identified in rice genome. Based on functional annotation of parental genes it was proposed that the circRNAs regulate gene expression by facilitating transcription, metabolic adaptation, signal transduction, and ion homeostasis-related pathways.<sup>[57]</sup> In sugar beet competitive endogenous function of circRNA revealed its involvement in copper redistribution, plasma membrane permeability, glycometabolism, energy metabolism and phosphoinositol signaling system.<sup>[58]</sup> Similarly, in *Populus euphratica* 14 identified circRNA have been found to enhance plant's tolerance to salt stress by targeting different pathways and regulating biological events like metabolism, hormone regulation, ion compartmentation, oxidative stress, and cell division.<sup>[59]</sup>

The macronutrients that are very crucial to plants are nitrogen (N), phosphorus (P), calcium (Ca), etc. An attempt was made to explore the role of circRNA in response to low N and P conditions.<sup>[60,61]</sup> Upregulation of circRNA has been reported in the soyabean crop in response to low P stress. Pathway enrichment study further indicated that circRNA host genes were involved in defense response, ADP binding, signal transduction, etc.<sup>[61]</sup> Similarly, wheat genome showed differential expression of 6 circRNAs in low N stress, suggest their role in signaling, responses to stimuli.<sup>[60]</sup> Recently, Ma et al.<sup>[62]</sup> also reported differentially expressed CircRNA under nitrogen deficient condition in maize genome. The identified circRNA could act as miRNA decoy and seemed to be involved regulating metabolic processes and organonitrogen compound biosynthesis. Ca<sup>2+</sup> deficiency in Cabbage revealed varying expression of 23 circRNAs having roles in cell wall metabolism, plant hormone signal transduction, ATPase activity, etc.<sup>[63]</sup>

Plant pathogens are considered a global threat that hampers overall food production, causing approximately 30% loss globally.<sup>[64-66]</sup> Viruses, bacteria, fungi are among the most important causal agents of infectious diseases in plants. To counteract the stress caused by these pathogens, plants employ different strategies like hormone-mediated defense, signaling response, regularization of metabolism, degradation of proteins, RNA mediated defense response, etc.<sup>[67]</sup> Besides, the role of circRNA has also been associated in relation to biotic stress. For example, in response to the fungal pathogen, the expressional variation of 34 circRNAs was explored in cotton. Parent gene investigation revealed that 20 out of 34 genes involve in stimulus response, confirming the role of circRNA in biotic stress.<sup>[68]</sup> *M. oryzae* triggered circRNAs in rice genome showed involvement in different biosynthetic pathways like terpenoid, stress-responsive, protein export, and other secondary

metabolites.<sup>[69]</sup> Likewise CircRNAs were also identified in rice genome upon bacterial infection caused by *Xanthomonas Oryzae*. Based on functional annotation of target mRNAs and host genes, circRNAs appeared to play important role in mediating rice responses to pathogen invasion by targeting different biosynthetic pathways related to chloroplast, peroxisome, photorespiration and diterpenoid biosynthesis.<sup>[70]</sup> In addition, the role of circRNA in imparting resistance to melon against gummy stem blight disease caused by fungus *Didymella bryoniae* has been elucidated. CircRNA displayed its role by targeting the genes that played important role in defense response of melon.<sup>[71]</sup> Similarly, CircRNA have been identified in melon in response to powdery mildew (PM) disease through comparative transcriptomic analysis. Functional annotation of CircRNA parental genes revealed its involvement in metabolic processes, oxidation reduction, and response to biotic stimuli thus indicating their regulatory mechanism in resisting PM.<sup>[72]</sup> Two circRNAs circRNA45 and circRNA47 were characterized in tomato genome that imparts immunity against *Phytophthora infestans* infection by sponging and regulating the expression of miR477-3P.<sup>[73]</sup> The role of circRNA and other non-coding RNAs has been described against Ginseng rusty root disease symptom (GRS) in ginseng plant. CircRNA exhibited its affect by altering fatty acid-related pathways.<sup>[74]</sup> *Pectobacterium corotvorum* brasiliense (Pcb) of Enterobacteriaceae causes soft rot and blackleg diseases in potatoes that hamper its production.<sup>[32]</sup> Zhou et al 2017, identified potato-Pcb responsive 429 differentially expressed circRNAs. Parental genes of this circRNA were involved in cell wall metabolism, defense response, ADP binding, pectin catabolic process, etc thus confirming the role of circRNA in response to biotic stress.<sup>[32]</sup> Similarly, 584 circRNAs were identified during *Pseudomonas syringae* (Psa) invasion in kiwifruit suggesting their role in plant-pathogen interaction. Further functional analysis of parent genes indicated their involvement in photosynthesis, signal transduction, and immune responses.<sup>[75]</sup> Furthermore, in response to viral pathogens, 83 circRNAs in tomato having a role in pathways like photosynthesis, signaling system, RNA transport, plant hormone, etc were identified by Wang et al 2018.<sup>[76]</sup> Several reports confirm the role of circRNAs in metabolism, cell regulation, response to biotic stress, etc. based on their binding capacity to miRNAs, which requires further wet-lab validations.<sup>[77]</sup>

### Future prospects

Extensive research has established the fact that circRNAs are stable molecules, enriched in different cells where they show variation in expression depending on the physiological conditions. In humans, several independent research confirmed the applicability of circRNAs as biomarkers, particularly in cancer diseases. However, in contrast to the animal system, there are no experimentally validated marker circRNAs reported in plants. Hence, based on their properties and advantages

offered over standard markers future research on the validation of circRNA as a biomarker in plants is an attractive research avenue. Properties including resistance to various enzymes, long half-life, and simple identification make the circRNA an exceptional molecule for monitoring crop yields, pathogens, and other research and practices in agriculture. In plants, several reports confirm the differential expression of circRNAs during varied physiological conditions. Despite numerous reports have elucidated the role of circRNA in plants with respect to stressful conditions the present knowledge on its functions and biogenesis is still elusive. Therefore, further studies need to be conducted or need to be carried out to provide crucial insights into the mechanism of circRNA functionality. Moreover, understanding the intricated regulatory aspect of circRNAs would be helpful in devising new strategies to combat physiological responses in plants toward biotic/abiotic stresses

### Conflict of interest

None declared

### Funding

Unfunded: The work was not supported by any national or international organization.

### Data availability

Information presented are cited properly.

### Acknowledgements

We are thankful to Department of Radiology, Medical Imaging Center, The Affiliated Hospital of Yangzhou University, Yangzhou University, Yangzhou, China and also Negenome Bio Solutions Pvt Ltd, India for providing the necessary facilities to carry out this review work.

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