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Circular RNAs as Molecular Sponges Modulating miRNA Activity in Cotton

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Abstract Circular RNAs (circRNAs) are a unique class of noncoding RNAs with covalently closed loop structures that play a crucial role in gene regulation in eukaryotes. In cotton (*Gossypium* spp.), microRNAs (miRNAs) are central to posttranscriptional gene regulation, influencing growth, development, and stress responses. This study investigates the role of circRNAs as molecular sponges in regulating miRNA activity in cotton. We first describe the biogenesis of circRNAs, their structural classification, and key features such as stability and tissue-specific expression. We then examine in detail the mechanisms by which circRNAs sequester miRNAs, including a competing endogenous RNA (ceRNA) network framework and experimental approaches to validate their sponging activity. We then highlight the regulatory roles of circRNAs in cotton fiber development, stress adaptation, and defense signaling through the circRNA-miRNA-mRNA axis. This study also reviews the progress in circRNA discovery using high-throughput sequencing and computational methods, as well as the challenges faced in their annotation. A key case study illustrates how specific circular RNAs act as "sponges" for miR156 and miR828, regulating SPL transcription factors and influencing fiber phenotype. Finally, we explore the potential of circular RNAs as biotechnological tools and molecular targets in cotton breeding programs. This study highlights the potential of circular RNA research for improving cotton quality and stress tolerance while also identifying knowledge gaps and future directions for multi-omics integration and genome editing strategies.

Keywords Circular RNA (circRNA); microRNA (miRNA) sponge; Cotton fiber development; Non-coding RNA regulation; Post-transcriptional gene regulation

1 Introduction

Circular RNA (circRNA) has actually been present in cells for a long time, but it is only in recent years that the scientific community has come to understand it. At first, it was regarded as a "product of error" in the editing process and no one paid attention. However, as research deepened, it was found that it not only exists universally in eukaryotes such as plants, but also varies in expression among different tissues, cell types, and even at different developmental stages. These features make people start to re-examine its role. Its structure is quite unique-unlike other RNAs that have A 5' cap and a 3' poly (A) tail, it is a closed loop. This structure makes it more stable and less prone to degradation. Precisely because of this, it can persist in cells and perform functions, such as "adsorbing" miRNA, serving as a protein binding platform, or regulating the expression of certain genes (Huang et al., 2020; Miysir et al., 2022).

When it comes to miRNA, it is another type of non-coding small RNA. Although it is short, it plays a key role in gene regulation. miRNA can bind to specific mrnas, rendering them dysfunctional or preventing them from being translated. Especially in cotton, miRNA has a significant impact-it is involved in both how the fibers grow and how the plants respond to external environmental stresses such as high temperatures and drought. If there are problems with miRNA regulation, the development and adaptability of cotton may be affected (Salih et al., 2021; Zhang et al., 2021).

Interestingly, there is also "interaction" between circRNA and miRNA. Many circrnas can absorb mirnas like "sponges", preventing them from seeking their target genes. This "interference" mechanism may have played a role in some key processes of cotton, such as fiber development or stress response. In other words, circular RNA is not an obscure "accompaniment". It may be one of the driving forces behind the regulation of these important agronomic traits (Benchi et al., 2023).

Therefore, what this study aims to do is to systematically review the current research on circRNA in cotton. We will cover how they are produced, how they are expressed at different developmental stages of cotton, and how they "interact" with miRNA. In addition, it is also hoped that we can explore whether these discoveries have any new inspirations or application Spaces for cotton breeding or future biotechnology.

2 Biogenesis and Characteristics of Circular RNAs in Plants

2.1 Mechanisms of circRNA formation

How is circular RNA formed? In plants, the currently known pathways for this process mainly include two types: reverse splicing and lasso cyclization. Among them, the reverse splicing path sounds like "going back"-the downstream 5 'donor site bypasses the middle region and directly connects to the upstream 3' receptor site, resulting in the formation of a closed RNA loop (Figure 1). This process is closely related to the familiar splicing mechanism, and RNA-binding proteins and long intron sequences are also often involved. However, plants are different from animals-in animals, there are often repetitive sequences or complementary sequences acting as "Bridges" at the splicing ends. But in plants, these regions are much cleaner and lack those reverse repetitions. This might mean that plants use another set of rules, or we haven't yet understood how they work (Zhao et al., 2019). As for the second mechanism-lason-driven cyclization, which is also called the "exon skipping" mode, it sounds a bit like an splicing error: skipping the middle section and processing the formed lason-like structure to obtain circular RNA (Zhang et al., 2020). Although it may not sound like the "right way", it does leave diverse traces in the plant transcriptome.

2.2 Classification of circRNAs

Not all circular RNAs look the same and are classified into several types based on their different sources. The most common type is exon circular RNA (ecircRNA), which is composed only of exon sequences and usually floats in the cytoplasm. Then there is the circular intron RNA (ciRNA), which is mainly composed of intron fragments and prefers to stay in the cell nucleus. There is also a "hybrid type" called exon-intron circular RNA (EIciRNA), which has both exon and intron components and is mainly active in the nucleus (Chen et al., 2017). These different types actually reflect the complexity of their generation processes and the functional roles they may undertake respectively.

2.3 Stability, conservation, and tissue-specific expression patterns in plants

One important reason why circular RNA has aroused the interest of researchers is that it is particularly resistant to "damage". Because the structure is closed, exonucases are difficult to swallow, which makes it much more stable than linear RNA (Chen et al., 2019). Among many plant species, we can also see the "presence" of the same circular RNA, which indicates that they have been preserved during evolution and may play certain key roles. But they are not "everywhere" either. The expression of circular RNAs is often selective, such as only appearing in certain tissues, specific cell types or developmental stages. Furthermore, some biological or abiotic stresses (such as drought and temperature changes) can also induce their expression (Tong et al., 2018). This specific binding stability makes one can't help but speculate that they might play a "key node" role in the plant regulatory system or could be very promising biomarkers in the future.

3 Mechanism of circRNA-Mediated miRNA Sponging in Cotton

3.1 Concept of miRNA sponges: base-pairing and sequestration of miRNAs

Can circular RNA regulate miRNA? The answer is affirmative. The key lies in the fact that its sequence usually contains multiple so-called "miRNA response elements (MRes)". These regions match up with miRNA and can "stick" miRNA through base pairing-just like a molecular-level "sponge" that isolates the originally freely moving miRNA. This isolation action may seem simple, but in fact, it disrupts the original plan of miRNA to bind to mRNA targets, thereby weakening its inhibitory effect on target genes. The final result is that mRNA is more easily translated, and gene expression is subsequently upregulated. However, whether it can truly "take effect" depends on several conditions: the circRNA itself must have a certain abundance, the number of Mres cannot be too small, and it also depends on whether its affinity for miRNA is sufficient. In addition, the specific state and environment of the cells also affect the performance of this "spongy effect" (Ren et al., 2020; Made et al., 2023).

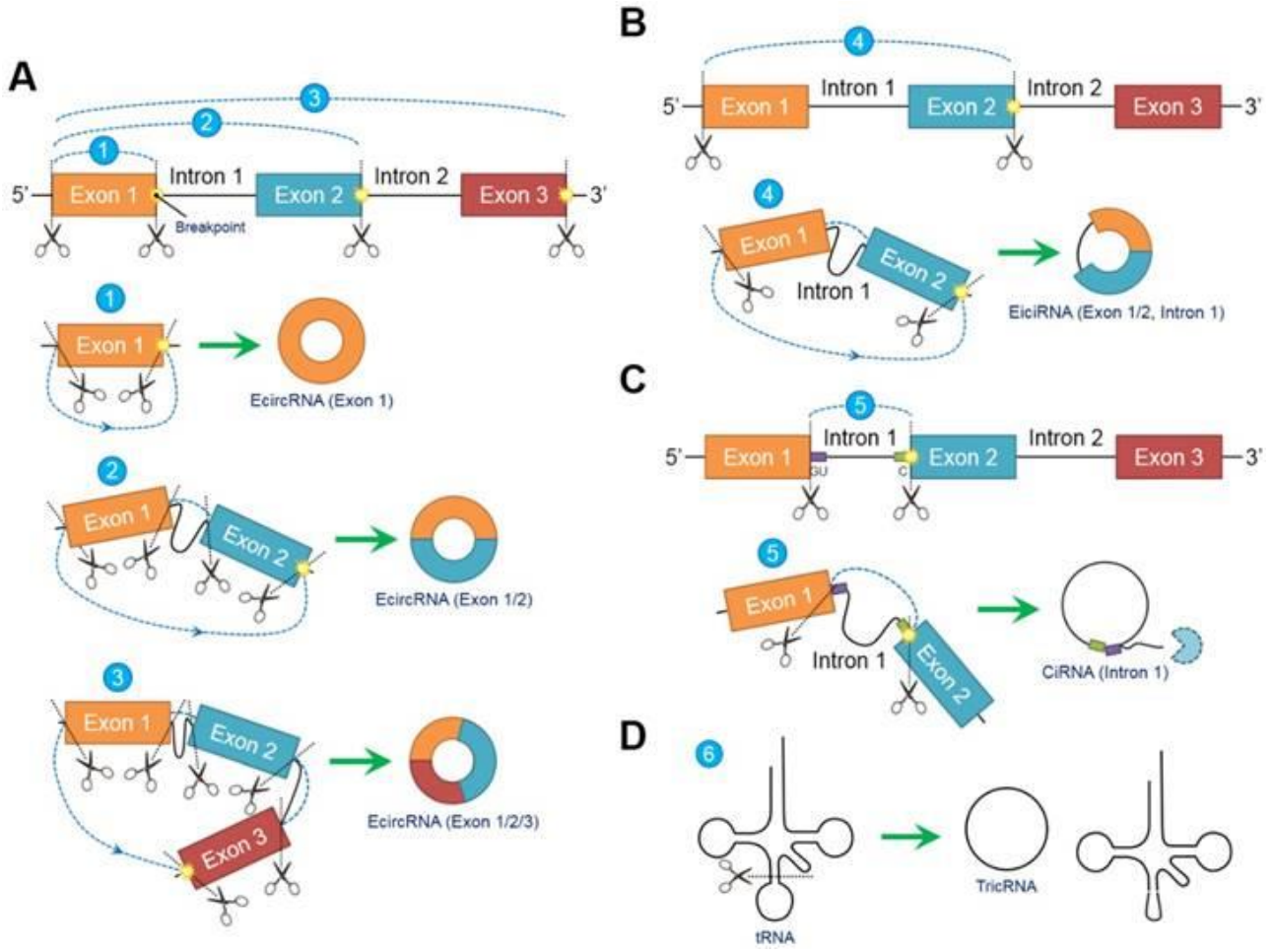

Figure 1 Biogenesis models of circular RNAs (circRNAs). Due to the emergence of differentially located breakpoints, primary RNA transcripts undergo “back-splicing” to produce the 5′ splicing donor site and 3′ splicing acceptor site. Subsequently, the 5′ splicing donor site is combined with the 3′ splicing acceptor site in reverse order to form a covalently closed loop without 5′ or 3′ polarities and poly (A) tails. (A) Exonic circRNAs (ecircRNAs) are composed exclusively of exons without flanking introns. The number of exons ranges from one to two or more depending on the breakpoints. Over 80% of circRNAs arise from ecircRNAs. (B) Exons (at least one) accompanied by flanking introns that have not been degraded during “back-splicing” compose exon-intron circRNAs (eiciRNAs). (C) Intron-derived circRNAs (ciRNAs) are produced through a lariat-derived mechanism depending on a consensus GU-rich domain near the 5′ splicing site and a C-rich domain near the breakpoint. The remaining noncircularized introns are sequestered. (D) tRNA intronic circRNAs (tricRNAs) originate from the exons and introns of pre-tRNAs cleaved by the tRNA splicing endonuclease complex. *Abbreviations*: ciRNA: circular intronic RNA; ecircRNA: exonic circRNA; eiciRNA: exon-intron circRNA; tricRNA: tRNA intronic circular RNA (Adopted from Chen et al., 2019)

3.2 CircRNA-miRNA-mRNA regulatory axis (ceRNA hypothesis)

It's not only circRNA that can participate in this kind of "competition". According to the ceRNA (Competitive endogenous RNA) hypothesis, mRNA itself, lncRNA, etc. may also, like circRNA, compete to bind to miRNA. They do not operate independently of each other but form a complex regulatory network by competing for miRNA together. The role of circRNA in this process is like a "molecular bait"-it does not directly regulate any genes itself, but it can influence the destination of miRNA and indirectly interfere with the expression of other RNAs (especially mrnas). This "detour regulation" approach has been found in plant development, environmental stress response, and even certain pathological states (Han et al., 2020; Schwarzenbach, 2024). Ultimately, this is a "fine-tuning mechanism" characterized by crosstalk, rather than a simple switch-mode regulation.

3.3 Experimental approaches to validate sponge activity

No matter how many theories there are, they all need experiments to support them. To prove that a certain circRNA is indeed "adsorbing" miRNA, researchers now commonly use several methods. The first is the

dual-luciferase reporter assay. This idea is relatively straightforward: Insert circRNA and miRNA together into an expression vector and observe whether the reporter gene activity changes. If there is a change, it indicates that binding has occurred between them (Yang et al., 2020). Then comes RNA immunoprecipitation (RIP). This step is like "molecular-level net pulling", using antibodies against Argonaute protein to pull out the miRNA-circRNA complex, thereby determining whether they are "in the same frame" (Yang et al., 2022). Finally, there is the RNA pull-down experiment, which is more like the "fishing method"-using biotin-labeled probes to catch the circRNA or miRNA of interest and see what kind of "fish" are caught (Bai et al., 2018; Singh et al., 2023). These methods are often used in combination, one to verify the structure and the other to supplement the function, confirming from different aspects the true role of circRNA in the miRNA regulatory network.

4 Functional Roles of circRNAs in Cotton Development and Stress Responses

4.1 Regulation of fiber development and elongation via miRNA sequestration

During the development of cotton fibers, circRNA is not an onlooker. Although experimental evidence regarding its direct involvement in such regulation is still accumulating at present, there are already many indirect clues suggesting that it may have been involved in this complex process. For instance, it can "intercept" specific mirnas through the ceRNA mechanism, reducing the inhibition of these mirnas on certain key mrnas, thereby influencing cell differentiation and growth. This mechanism has long been reported in other plants, and in cotton, circRNA shows obvious expression dynamics and stage specificity at different developmental stages, which further suggests that it is not insignificant. For instance, some studies have identified that certain circRNA-miRNA-mRNA networks have tissue-specific expression patterns during the cotton fiber formation period (Li et al., 2024). So, even though many details have not yet been fully revealed, the role of circRNA in fiber growth seems to be increasingly difficult to ignore.

4.2 circRNA-mediated modulation of abiotic stress responses (e.g., drought, salt)

When plants encounter abiotic stresses such as drought or high salt content, their internal gene expression networks often adjust rapidly. Cotton is no exception. Some recent studies have shown that the expression of circRNA is not stable under these stress conditions and instead undergoes significant changes. In other words, their existence seems to be "related" to environmental changes. Take drought as an example. By using deep sequencing technology, scientists have discovered that some circrnas are involved in the ceRNA regulatory network of specific tissues and even specific varieties. This type of circRNA can adsorb miRNA, thereby affecting the expression of certain stress response genes (Yadav et al., 2024). A widely mentioned example is circ125 and miR7484b/miR7450b, which may have constructed a new regulatory relationship in the context of drought. This also indicates from one aspect that circRNA may play a certain role as a "regulator" in the adaptation to abiotic stress, and this role is highly context-specific and complex.

4.3 Role of circRNAs in disease resistance and defense signaling

Similar to environmental stress, the invasion of pathogens can also trigger a series of molecular reactions within cotton. Interestingly, circRNA also "came to life" at this time. In a study on Fusarium wilt, researchers observed that hundreds or thousands of circrnas were differentially expressed in different cotton strains after infection (Xiang et al., 2018). Some circrnas are significantly activated in disease-resistant strains, but not so obviously in susceptible strains. What is more notable is that many of these circrnas are related to NBS genes, and the NBS gene family is precisely a core member of the plant immune response. This discovery suggests that circRNA may not directly interact with pathogens but indirectly affect the expression of downstream immune-related genes by regulating the activity of miRNA. This regulatory approach adds a new level to the plant's defense mechanism and also opens up a new breakthrough for enhancing the disease resistance of cotton.

5 High-Throughput Identification and Profiling of circRNAs in Cotton

5.1 RNA-seq and bioinformatic pipelines (e.g., CIRI, find_circ)

When looking for circular RNAs in cotton, RNA sequencing is usually an indispensable step, especially for the version after the rRNA has been removed. However, light sequencing is not enough; some specialized bioinformatics tools are also needed to "dig out" circular RNAs from the data. Programs like CIRI and find_circ

are designed to identify the connection points of reverse splicing, as this type of splicing method is unique to circRNA. However, the performance of different tools varies and is not completely uniform. Some studies have compared CIRI, find_circ, CIRCexplorer, etc., and found that their results were quite consistent when identifying highly expressed circrnas. However, when encountering low abundance or special types, there would be differences, and even false positive results specific to the tools themselves would occur (Hansen, 2018). Therefore, many studies will adopt a compromise approach-integrating the results of several tools to enhance the overall reliability. In multiple developmental stages and varieties of cotton, this type of method has detected hundreds and thousands of circular RNAs.

5.2 Databases and repositories of plant circRNAs, including cotton-specific resources

At present, for the study of circular RNA in plants, the database is passable, but it is still far from being "perfect". In fact, many databases are borrowed from animals. There are not many that are specifically designed for plants, let alone for cotton. However, some resource libraries do already cover the circular RNA data of cotton, as well as that of other crops. This type of resource not only integrates RNA sequencing data, but also incorporates the predicted circular RNA sequences and annotation information, which is helpful for subsequent functional studies and cross-species comparisons (Gao and Zhao, 2018). Although their coverage is still limited at present, they at least provide researchers with a starting point to enter.

5.3 Challenges in accurately annotating and quantifying circRNAs in complex genomes

It is indeed quite difficult to accurately annotate and quantify circrnas in plants with complex genomes like cotton. The problem is not one or two, but the accumulation of multiple factors. For instance, cotton is polyploid, with high sequence similarity in many regions of the genome and a large number of repetitive elements, which makes the localization of reverse splicing sites tricky (Zhao et al., 2017). Furthermore, algorithms are not omnipotent. Different tools often have poor recognition ability for low-expression and atypical splicing circrnas and may even report errors (Dong et al., 2023). What is even more troublesome is that some genomes themselves are not fully annotated, especially the circRNA reference set for plants, where the available information is relatively limited, making it extremely difficult to predict from scratch and compare across samples. Moreover, circular RNAs and linear transcripts often overlap, and with their different expressions in various tissues and under different conditions, it becomes difficult to conduct accurate quantitative analysis. Nowadays, many studies are attempting to adopt combined strategies, such as improving annotations, developing reference resources specifically for cotton, or integrating the recognition results of multiple tools, to enhance the quality of analysis. These works are precisely the key directions of current research.

6 Case Study

6.1 Identification of key circRNAs acting as miR156/miR828 sponges in fiber cells

When studying the regulatory network of cotton fiber development, in the past, almost all attention was focused on miRNA. However, with the continuous advancement of high-throughput sequencing technology and bioinformatics tools, researchers have begun to turn their attention to those "overlooked roles"-such as circrnas. In fact, studies have found that in cotton fibroblasts, there are some circrnas that may have binding sites for miR156 or miR828. These two mirnas are highly expressed during the initiation and elongation stages of fibers, and are closely related to several key developmental transcription factors (such as SPL and MYB families) (Wang et al., 2017). Although there is currently a lack of direct experimental evidence to fully prove that certain circrnas can indeed "attach" to miR156/miR828, from the perspective of sequence prediction and expression patterns, this possibility is not groundless. Especially in specific fibrous tissues, the existence of multiple circrnas with potential binding sites for these mirnas is already quite revealing in itself.

6.2 Impact on downstream target gene expression

When it comes to the regulation of circRNA, it is impossible to avoid its influence on downstream target genes. Especially the two transcription factors, SPL and MYB, they directly determine how fibroblasts differentiate, elongate, and even the efficiency of secondary wall synthesis. Mirnas like miR156/157 usually "target" the SPL gene and inhibit its expression. However, once such mirnas are adsorbed by circrnas, the expression of SPL will

be released, resulting in more favorable fiber extension (Kwak et al., 2009). Similarly, miR828 targets the MYB gene related to hair and fiber development, and the logic is similar. So, if certain circrnas "intervene" at critical moments, they may be able to influence the expression of these developmental regulatory factors, ultimately affecting the quality and yield of cotton fibers.

6.3 Functional validation and phenotypic consequences in overexpression/knockdown lines

Not all speculations are reliable; experiments have to speak for themselves. Take miR156/157 as an example. Experiments have shown that if its function is artificially inhibited, the length of cotton fibers will significantly shorten, which is sufficient to demonstrate their importance in fiber elongation (Figure 2) (Liu et al., 2014). However, it should be noted that there are currently few studies on the overexpression or knockdown of specific circrnas directly in cotton fiber cells. The evidence in this regard is indeed insufficient. However, the existing results of ceRNA network construction and the phenotypic changes after miRNA functional intervention are actually suggesting that circRNA's regulation of miRNA through "spongization" may have a substantial impact on the developmental process. Next, if the levels of circRNA can be further controlled through transgenic technology, perhaps their true "weight" in the development of cotton fibers can be more clearly defined.

7 Biotechnological and Breeding Implications of circRNAs in Cotton

7.1 Potential of circRNAs as novel molecular markers or regulatory targets

Finding suitable molecular markers in cotton breeding has always been an old problem. Although traditional marking techniques are mature, they are sometimes not precise enough, especially when dealing with complex traits. Now, circRNA has begun to come into the view of researchers, and the reasons are not complicated: it is stable, not easily degraded, and the amount expressed in which tissue and at which developmental stage varies significantly. It is precisely these characteristics that have led people to start considering-could circRNA be regarded as a new type of marker candidate? Especially during key processes such as drought stress or fiber formation, the expression patterns of some circrnas will change significantly (Zhang et al., 2024), which undoubtedly opens up new ideas for screening related agronomic traits. Furthermore, it is not merely a "mark". Some circrnas can also adsorb mirnas, thereby affecting gene expression, which indicates that they themselves have regulatory value. If those circrnas related to agronomic traits and conserved in multiple cotton varieties can be identified, perhaps they can also serve as targets and directly participate in breeding design.

7.2 Engineering circRNA expression for improving fiber quality or stress resistance

Not all circrnas are useful, but some of them are indeed "well-managed". Circrnas that can bind to mirnas and happen to occur in fibrous development or adverse response have become potential intervention targets. Through genetic engineering methods, such as overexpressing a certain circRNA or knocking it down-it is possible for us to indirectly regulate the activity of miRNA and further regulate those genes related to development or resistance (Li et al., 2023). For instance, some studies have mentioned that regulating the circRNA network related to drought response might be a strategy to enhance the stress resistance of cotton. Of course, this method is not intended to completely replace traditional breeding. It is more like a "reinforcement": on the basis of the existing genetic background, it fine-tunes key regulatory points to enhance specific traits, rather than redesigning the entire cotton plant.

7.3 Integration of circRNA knowledge into precision cotton breeding strategies

Introducing circRNA into the precision breeding system may sound complicated, but the logic is actually very simple. High-throughput sequencing has already been able to help us identify which circrnas are highly expressed in good varieties and which ones are closely related to stress responses. The next thing is how to make good use of this information. The existing plant circRNA database is currently expanding. Once sufficient resources are accumulated, breeders can fully transform this information into practical operations, such as designing molecular marker-assisted selection programs or directly conducting genome editing at circRNA sites (Zhu and Luo, 2024). The ultimate goal is not to create a gimmick, but to screen out genotypes with more efficient regulatory networks and better trait expression. However, now there is a new perspective-no longer just looking at linear genes, but also beginning to pay attention to those RNAs that have gone in a "circle".

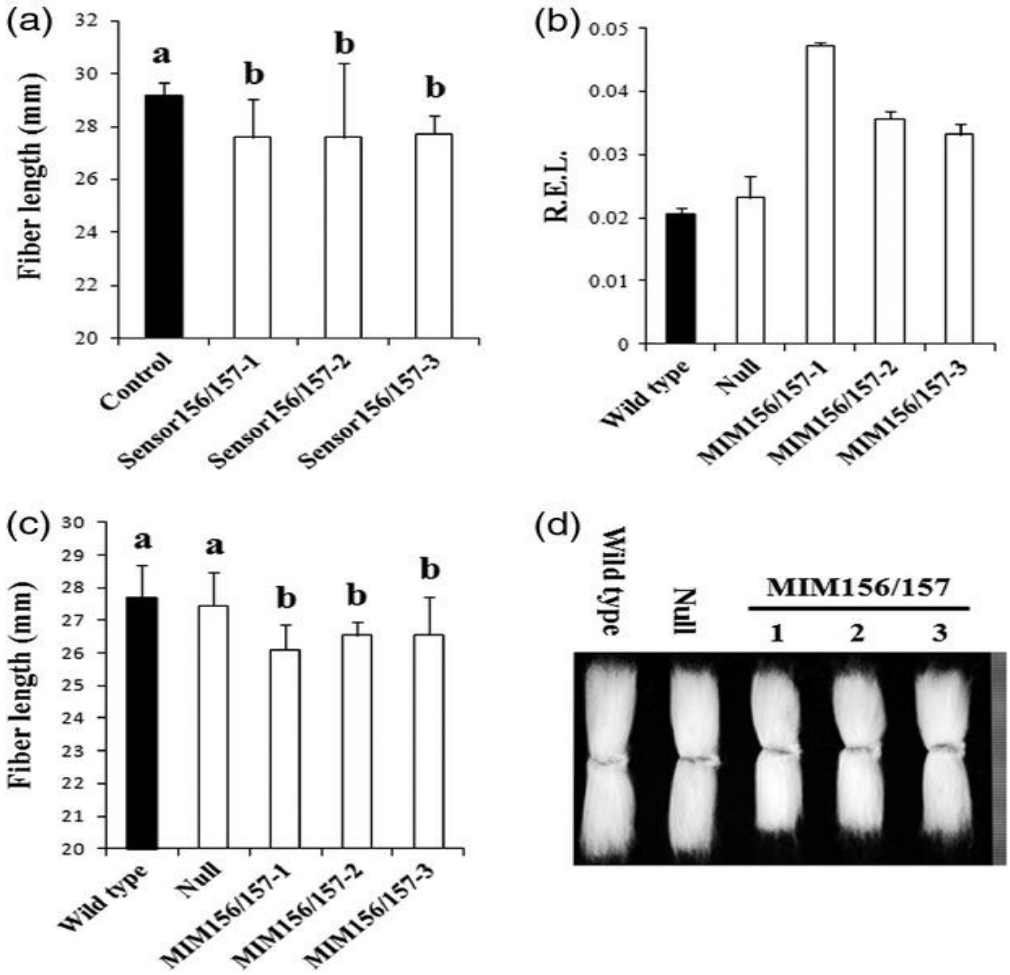

Figure 2 Reduced Gb-miR156/157 expression suppresses fiber elongation. (a) The mature fiber length of the samples planted in green house (2012) was measured manually with a comb. Control, transgenic plants containing the construct without the miRNA reverse complement site. Sensor156/157, transgenic plants of Gb-miR156/157 reverse complement site. (b) Relative expression of the Gb-miR156/157 target (TC253516) in fibers (12 DPA). R.E.L., the relative expression levels were calculated using GhUBQ7 as a control. (c) The mature fiber length of the samples planted in the experiment field (2013) was measured manually with a comb. Null, segregated nontransgenic plants derived from the three transformants MIM156/157-1, -2 and -3. MIM156/157, plants transformed with the miR156/157 mimicry vector. (d) The image of mature fiber. Error bars (a, c) represent standard deviation of samples from at least 20 ovules. Different letters in (a) and (c) indicate statistically significant differences at $P < 0.05$ based on analysis of variance (anova) (Tukey's Multiple Comparison Test). The error bars (b) indicate the standard deviation of three biological replicates (Adopted from Liu et al., 2014)

8 Concluding Remarks and Future Perspectives

In cotton, is circRNA really the key regulatory factor? From the existing research, it is indeed involved in many important processes, especially in development and stress responses. It can adsorb miRNA, temporarily isolate these "small molecule regulators", and thereby affect the expression of target genes. This effect has been observed in multiple tissues and varieties. Especially under drought conditions, the "game relationship" among circRNA-miRNA-mRNA becomes more complex and even has a certain variety specificity. For instance, circ125 can bind to miR7484b and miR7450b and is believed to possibly play a certain regulatory role in stress adaptation. Although such discoveries are still rare, they have already begun to prompt us to rethink the "presence" of circrnas.

Of course, many problems remain unsolved. At present, the role of circRNA-miRNA that has been truly verified through experiments is still very limited, and more is just prediction. As for whether these predictions are reliable or not, it still depends on whether conclusive evidence can be found in the future. The explanatory power of computational models is limited, and sometimes it is hard to tell whether it is a real biological interaction or an

"illusion" brought about by data analysis. Moreover, are circrnas also involved in other physiological processes? How conservative is it among different cotton varieties? Could it serve as a genuine breeding target in the future? All of these still need to be further explored.

What should be done next? Instead of merely verifying a single circRNA, we need to broaden our perspective a bit. Only by integrating data from different levels such as the transcriptome, proteome, and epigenome can a more complete regulatory network diagram be constructed. Some new models in the field of artificial intelligence, such as Transformer and graph neural networks, may help us make faster progress in predicting novel circRNA-miRNA pairings. In addition, genome editing tools like CRISPR and synthetic biology technologies may also become powerful tools for manipulating the expression of circrnas in the future. It is used for verification and also for improving varieties. If combined with the expansion of the plant circRNA database and the establishment of a unified experimental procedure, the development pace in this field is expected to accelerate further.

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Conflict of Interest Disclosure

The author affirms that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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