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Analysis of the Regulatory Network of Cotton Fiber Development Based on Transcriptomics and Epigenomics

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Abstract Cotton fiber development represents a distinctive model of plant cell elongation and differentiation. In this study, we systematically analyzed the regulatory network underlying cotton fiber development by integrating transcriptomic and epigenomic data. Temporal expression profiling revealed stage-specific gene expression during fiber initiation, elongation, and maturation, with key transcription factors such as MYB, NAC, and bHLH playing pivotal roles. Non-coding RNAs including lncRNAs and miRNAs were also identified as important regulators of post-transcriptional gene silencing. Epigenomic analyses uncovered dynamic DNA methylation patterns and histone modifications correlating with fiber-specific gene activity, alongside changes in chromatin accessibility and 3D genome architecture during development. Through multi-omics integration, we constructed regulatory networks highlighting co-expression modules, signaling pathways, and environmental responses, and validated these networks using a case study on *Gossypium hirsutum*, focusing on the GhMYB25-like-centered cascade. Our results underscore the complexity of gene regulation in fiber development and suggest that advanced technologies such as single-cell omics and CRISPR-based validation will further refine our understanding and enable molecular breeding strategies to enhance cotton fiber quality and yield.

Keywords Cotton fiber development; Transcriptomics; Epigenomics; Gene regulatory network; Multi-omics integration

1 Introduction

The development of cotton fiber is a typical example of the elongation of a single plant cell, which provides a good research object for us to understand how cells grow, how they differentiate, and how cell walls are formed. The whole process can be divided into several different stages, such as how fiber cells start, how they elongate rapidly, and how secondary cell walls are formed later. These stages are affected by many genetic and epigenetic factors, which affect the quality and yield of cotton fiber (Li et al., 2020; Prasad et al., 2022; Bao et al., 2023). The process of controlling fiber development is a very complex regulatory system, which includes various transcription factors, gene modules, and signal transduction pathways. They work together to regulate the expression of thousands of genes and metabolites, which will affect traits such as fiber length and strength. Recent studies have shown that coordination between subgenomes and some special regulatory regions play a major role in fiber initiation and elongation, while non-coding RNA and epigenetic modifications also affect gene expression (You et al., 2023; Liu et al., 2024; Wang et al., 2024; Yang et al., 2024).

In the past, we did not have a detailed understanding of gene expression and chromatin changes during cotton fiber development. Now the situation is different. High-throughput transcriptome and epigenomic technologies have opened up this field. Whether it is RNA sequencing, eQTL positioning, or DNA methylation and chromatin accessibility analysis, once these tools are used together, we can see a lot more. For example, some previously unnoticed regulatory factors, transcription factors, and epigenetic markers related to fiber traits can now be identified. Interestingly, genetic variation and epigenetic variation do not work alone. They may play their own roles, or they may restrain or cooperate with each other at certain stages, and finally show the diversity of fiber phenotypes. For breeding, this is a rare breakthrough (Xiong et al., 2024; Zhao et al., 2024).

Our research is not to discover any new mechanism from scratch, but to string together the existing fragmented knowledge. The focus is on integration, not just telling a "omics" story, but combing the research results related to

transcriptomics and epigenomics together. What we want to understand more is which molecular mechanisms are at work during the fiber initiation and elongation process, which genes are the key control points, and which pathways are worth paying attention to. Of course, we are not just at the level of understanding. Later we also talked about whether these mechanisms can be used in practice, for example, by regulating certain specific genes or epigenetic sites, is it possible to make cotton fibers longer, stronger, and have a higher yield.

2 Transcriptomic Insights into Fiber Development

2.1 Temporal expression profiling of key genes during fiber initiation, elongation, and maturation

The development of cotton fiber is a complicated process from initiation to maturity. Now that the technical conditions are good, especially the development of spatial transcriptome and single-cell transcriptome, researchers can finally "separate and look", and analyze the gene expression in the development process in more detail by time period and cell. Not all genes are the same. Some "emerge" in the early stage, such as *SVB*, *SVBL*, *DOX2*, *KCS19.4*, and *BEE3*, which are closely related to the formation of cell walls (Figure 1) (Tuttle et al., 2015; Sun et al., 2025). But when the fiber transitions from the elongation stage to the synthesis of the secondary cell wall, the overall pattern of gene expression changes again. In other words, if the sampling time is not accurate, many important regulatory details will not be seen.

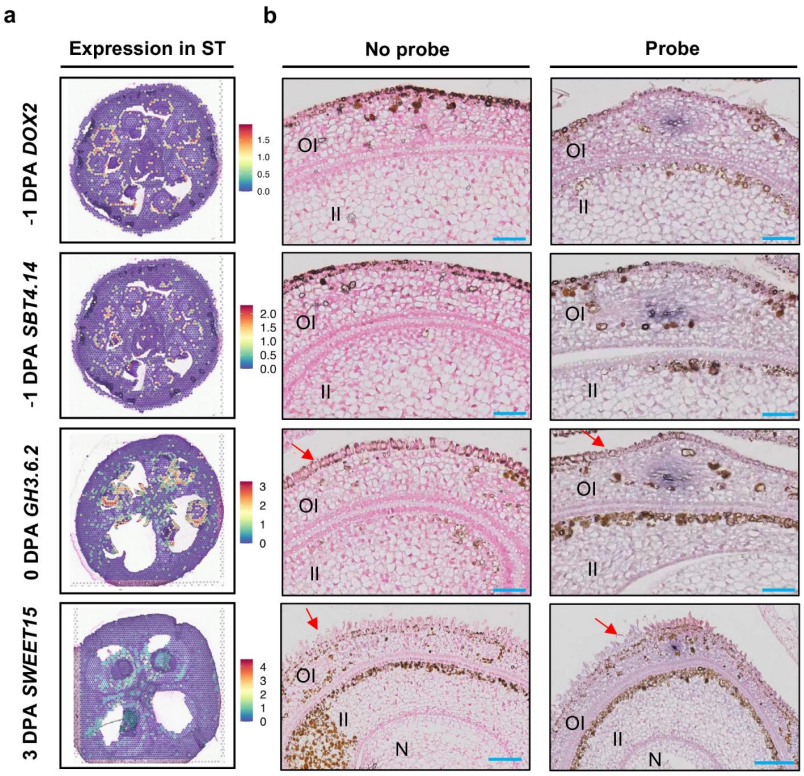

Figure 1 a Spatiotemporal expression pattern of *DOX2*, *SBT4.14*, *GH3.6.2*, and *SWEET15*, the marker genes of integument cells based on spatial transcriptomics. The color intensity indicates the relative transcript level of each marker gene. b Nitro-blue tetrazolium-stained RNA ISH shows the spatiotemporal expression patterns of *DOX2*, *SBT4.14*, *GH3.6.2*, and *SWEET15*. No probe was used as a blank control. The positive cells are stained bluish-violet. The data shown are representative images of three independent experiments with similar results. OI, outer integument; II, inner integument; N, nucellus. Red arrows indicate fiber cells. Scale bars, 50 μm in - 1 DPA and 0 DPA; 100 μm in 3 DPA (Adopted from Sun et al., 2025)

2.2 Identification of transcription factors (e.g., MYB, NAC, bHLH) regulating fiber traits

When it comes to the "commanders" who control fiber traits, transcription factors are definitely the highlight. MYB, NAC, and bHLH are often seen in research. Among them, GhMML3_A12 is a representative, which has been shown to be directly related to cotton fiber formation (Zhang et al., 2022). But we can't just focus on this one. Some other transcription factors are also closely related to specific gene modules at certain developmental stages, which in turn affect the quality and yield of the fiber. How do they work? Basically, they regulate cell elongation,

cell wall synthesis, and response to external pressure. These regulatory proteins together form a very complex network responsible for regulating various aspects of fiber development (Prasad et al., 2022; You et al., 2023).

2.3 Role of non-coding RNAs (e.g., lncRNAs, miRNAs) in post-transcriptional regulation

Although transcription factors are often mentioned, non-coding RNA is not idle either. In the development of cotton fiber, "behind-the-scenes roles" such as lncRNA and siRNA also participate in regulation. Studies have found that there are thousands of lncRNA transcripts with different expression patterns at different stages, indicating that they are not "spectators" during the fiber initiation and elongation stages (Zou et al., 2016). More interestingly, some small RNAs are derived from natural antisense transcripts (NAT), which can directly cut mRNA and thus change gene expression. For example, GhMML3_A12 itself will be regulated by an siRNA, which is equivalent to a "self-pruning" operation (Wan et al., 2016). These findings show that post-transcriptional regulation is also a link that cannot be ignored, and its role is not necessarily less than that of transcription factors.

3 Epigenomic Regulation in Cotton Fiber Cells

3.1 DNA methylation patterns and their correlation with fiber-specific gene expression

During the development of cotton fiber, DNA methylation, especially CHH type methylation, will gradually increase. This change is related to the differentiation of fiber cells and the expression of related genes. This methylation process is mainly completed through a pathway called H3K9me2, not through RNA-guided DNA methylation (RdDM). At the same time, this methylation is also related to the synthesis of lipid substances and the regulation of gene expression of reactive oxygen species, both of which are very important for fiber differentiation.

3.2 Histone modifications (e.g., H3K4me3, H3K27ac) and chromatin accessibility

During the development of fiber cells, histone modification and chromatin openness are critical. By studying the distribution of nucleosomes, scientists found that during the maturation of fiber cells, chromatin changes from a more active state to a less active state, and this change also affects the location of methylation on DNA, thereby affecting gene expression. "Active" marks such as H3K9me2 are associated with enhanced DNA methylation and the regulation of fiber-related gene expression (Wang et al., 2016). Through single-cell ATAC-seq technology, researchers have discovered some regulatory regions that only work in fiber cells, such as TCP pattern sequences, which can bind to transcription factors to regulate the rhythm of gene expression and metabolic activity during fiber growth.

3.3 Chromatin remodeling and the 3D genome organization in fiber developmental stages

Chromatin is not always the same. Especially at different stages of cotton fiber cell development, it will become more open, or on the contrary, more compact. There are actually many details behind this. For example, the position of nucleosomes is not fixed, but moves at certain key time points, so that chromatin gradually changes from the "on" state to the "off" state. But this structural change is not just a physical swing, it is often related to some deeper regulatory mechanisms-such as the establishment of DNA methylation patterns, and those gene expression programs that control cell differentiation and fiber elongation will also be affected. However, not all changes can be seen directly. After analyzing the openness of chromatin and gene expression data together, the study found that those special regulatory regions in the three-dimensional structure actually play a very critical role in regulating "when and where" genes are activated (Wang et al., 2023). In other words, these regions are like switch boxes. If they are not turned on, genes may remain silent. DNA methylation, histone modification, chromatin structure adjustment-they work separately and cooperate with each other. These epigenetic mechanisms are built up layer by layer, jointly determining which genes should play a role and which genes should be temporarily "dormant" during the development of fibroblasts. Overall, the regulation is rhythmic and hierarchical, rather than random.

4 Integrated Transcriptome-Epigenome Analysis

4.1 Correlating differentially expressed genes with epigenetic landscapes

Analyzing transcriptome data and epigenomic data together can more clearly show the relationship between changes in gene expression and some epigenetic modifications (such as DNA methylation and chromatin

openness). This approach allows researchers to find out which epigenetic state affects certain fiber-related genes, whether they are activated or inhibited, so as to have a more comprehensive understanding of the regulatory process during cotton fiber development (Ruprecht et al., 2024). For example, using high-resolution data to analyze chromatin openness and gene expression together can help reveal which epigenetic marks are related to gene activity, and also know their changing relationship in time and space (Zhang et al., 2023).

4.2 Predicting regulatory networks through multi-omics data integration

In fact, at the beginning, many regulatory relationships are not clear when looking at transcriptome data alone. In addition, the information of the epigenome is often scattered, and there are many places where data is missing. Relying on one data type alone cannot give a full picture. At this time, putting different "omics" data together, such as transcriptome and epigenetic maps, can actually piece together a more complete picture. Although it is not easy to operate, some new computational methods, such as unsupervised learning tools such as scAI, can indeed integrate these sparse data and help us straighten out the previously chaotic signals (Kartashov and Barski, 2014; Jin et al., 2020). However, don't expect these methods to be in place in one step. What they can do is to provide a sense of direction. For example, where may there be key transcription factors? Which non-coding RNA has regulatory functions? Which areas are worth focusing on? These integrated analyses can pull clues out from a large number of complex signals. Although it cannot directly explain all the mechanisms, it does help us move one step forward in the matter of fibroblast differentiation (Bahrami et al., 2024).

4.3 Insights into stage-specific activation and repression of fiber genes

Whether a gene is "on" or "off" is not entirely a matter of subjective guessing. Now there is a way to see this more clearly. When the two types of data, transcriptome and epigenome, are analyzed together, many patterns hidden behind the timeline can be seen. Which genes are turned on at which stage and when they are turned off can all be organized into a map. But there is a premise: these regulations are not necessarily simple and repetitive. Epigenetic mechanisms such as histone modification and DNA methylation have different combinations at different stages. Sometimes the impact is large, and sometimes the impact is not obvious. This is related to the "rhythm" of cotton fiber from the beginning, elongation to maturity (Lister et al., 2008; Marconett et al., 2013). In other words, understanding these stage changes is not just to satisfy scientific curiosity, it may also point to a very practical direction-we may be able to adjust fiber traits step by step to a better state through gene regulation. The key is that we must first understand "who is responsible and when".

5 Functional Modules and Regulatory Networks

5.1 Key hubs and modules identified through gene co-expression networks (WGCNA, etc.)

To put it simply, the co-expression network is to pull genes that are "often expressed together" together to see if they are doing the same thing. Methods like WGCNA have indeed helped us dig out some interesting modules from thousands of genes. For example, a previous study divided more than 13 000 genes with different expressions into several groups according to tissue type. The MEblack module is relatively prominent. It is rich in genes related to cell wall formation and is also related to fiber length (Ma et al., 2024). However, not every module has a "commander". Genes like *GhKCS1b_Dt* and *GhTUB5* are quite special. They play a significant role in controlling fiber elongation and are in a relatively core position in the entire network. There is also a point that is easily overlooked - in polyploid cotton, genes are not evenly divided. Studies have found that the contributions of the two subgenomes A and D to the network are not equal. In particular, some transcription factors in the A subgenome have more obvious regulatory effects (You et al., 2023; Xiong et al., 2024).

5.2 Signaling pathways involved in fiber elongation

Whether the fiber can grow fast and well is not determined by a single signaling pathway. Auxin, ethylene, brassinolide-they are all involved. Through KEGG analysis, researchers found that some genes involved in fatty acid elongation and hormone signaling are regulated to varying degrees at different developmental stages (Liu et al., 2024). These changes are not "automatic", but are related to the participation of regulatory modules and specific transcription factors. For example, some modules are particularly sensitive to specific hormones and can control the expression of key genes in cotton fibers, thereby affecting subsequent developmental processes (Bao et al., 2023).

5.3 Network rewiring under environmental and hormonal cues

The environment is changing, and the regulatory network will certainly not remain unchanged. Take water stress as an example. The JAZ1a module is manifested under this pressure, and it can mobilize a group of genes related to stress response (You et al., 2016). In addition to the environment, hormone signals will also "manipulate" the network structure. Some transcription factors related to hormone response will be integrated into the regulatory module, causing the entire network structure to adjust. Other studies have combined chromatin openness and gene expression and found that these environmental and hormonal factors can actually directly affect which fiber-related genes will be turned on and which will be temporarily closed (Chen et al., 2023). From these analyses, it can be seen that the regulatory system of cotton fiber is not a rigid model, but a dynamic system composed of multiple functional modules, which will change continuously according to internal and external conditions. The modules are interconnected, and the relationship between the central gene, signal pathway, and environmental factors is also quite complex, but it is these changes that jointly determine the final characteristics of cotton fiber.

6 Case Study: *Gossypium hirsutum* Fiber Development Network

6.1 Integration of RNA-seq and ChIP-seq data to identify regulatory circuits

RNA-seq alone can actually reveal a lot of things. For example, in different developmental stages of upland cotton, researchers have discovered thousands of genes with significantly different expressions through transcriptome analysis, some of which are transcription factors, and some are key players related to metabolism or signal transduction (Zhang et al., 2022). These genes may not play a role alone, but they are indeed inseparable from fiber growth. However, if you want to figure out how it is regulated, these expression data alone are not enough. At this time, co-expression network analysis tools such as WGCNA come in handy. It can screen out modules and central genes related to fiber traits, at least it can help us straighten out the threads and provide a general direction for the subsequent construction of regulatory pathways (Jiao et al., 2023). As for ChIP-seq, some studies use it a lot, while others have not been developed too much. Although the current literature does not systematically explain how RNA-seq and ChIP-seq can be used together, this does not hinder the research from moving forward. As long as the high-throughput sequencing results and network analysis are integrated, we can indeed see some clear maps, especially in understanding the regulatory mechanisms specific to cotton fibers, where signs have begun to emerge.

6.2 Dissection of the GhMYB25-like-centered regulatory cascade in fiber initiation

GhMYB25-like genes are a very important core factor in the development of upland cotton (*G. hirsutum*) fibers. Some co-expression network studies have found that transcription factors such as MYB and bHLH are critical "pivot points" in the initiation and elongation stages (Figure 2) (Yang et al., 2021). These transcription factors regulate genes related to cell wall synthesis, cytoskeleton arrangement, and hormone conduction, thereby affecting the differentiation and growth process of fiber cells at the beginning of development.

6.3 Validation of network predictions through gene knockout and overexpression

Scientists have verified the predicted regulatory networks through gene knockout and overexpression experiments. For example, some genes that are considered to be "hubs" encode actin, Rho GTPase activating proteins or specific transcription factors, which have been verified experimentally, indicating that they are indeed involved in fiber development (Zou et al., 2019). For example, after overexpressing the candidate gene GhTPR, it was found that the roots of Arabidopsis thaliana became longer, which supports the regulatory role of GhTPR in cotton fiber elongation (Xiao et al., 2023). These experimental methods provide very direct evidence that the genes and modules predicted in the network are indeed related to the biological processes of cotton fibers.

7 Challenges and Knowledge Gaps

7.1 Limited spatial resolution of transcriptomic and epigenomic profiling in fiber cells

Technology is changing, and research methods are becoming more and more detailed, especially in the field of single cells and spatial transcriptomes. It seems that there has been a lot of progress, but it is still a bit early to really understand the spatial expression pattern of cotton fiber cells clearly. The problem is not just whether the

tools are accurate enough. What is more troublesome is that the differentiation process of fiber cells is complex in itself. Sometimes the same cell group expresses completely different genes at different developmental stages. With existing technology, it is difficult to capture these changes and their precise location in the tissue at the same time. In other words, we know there is a change, but we don't know where it occurs; or we can see what is expressed, but we don't know which type of cell is responsible. This vague state directly affects our understanding of how cell types are specifically regulated (Fang et al., 2018).

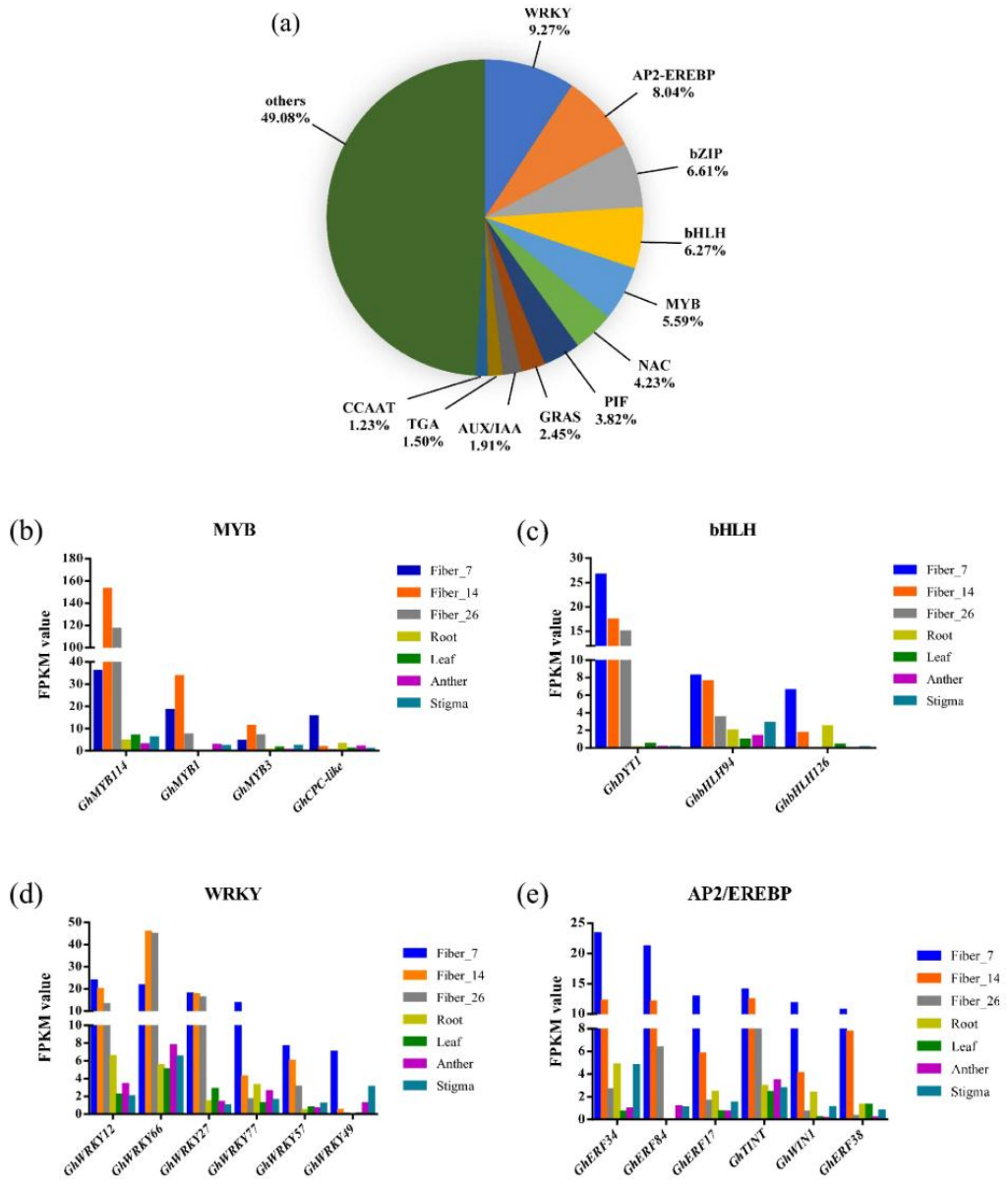

Figure 2 Statistics of transcription factor expression in different tissues of cotton. (a) Quantity and classification of transcription factor families. A total of 1 467 different transcription factors were annotated in 46 transcription factor families. The numbers represent the percentages of transcription factor genes. (b-e) Detailed illustration of the expression of transcription factors related to fiber elongation and development. The x-axis indicates the distribution of transcription factors in seven different tissues of cotton. The y-axis represents the FPKM value of each transcription factor in different tissues (Adopted from Yang et al., 2021)

7.2 Need for high-quality, cell-type-specific epigenomic maps

Many times, we don't actually lack data. The problem is that most existing epigenomic maps come from "mixed samples", that is, the average level measured by mixing many types of cells together. For fibroblasts, this information is not accurate enough. Their respective chromatin states and their own unique regulatory patterns are all obscured. What is really lacking now is a "single perspective" map for different types of fibroblasts at different

developmental stages. Without this, it is difficult for us to link specific epigenetic marks with specific gene regulation or trait expression. In other words, the clues are not absent, but they are "blurred" (Naoumkina and Kim, 2023).

7.3 Technical and computational challenges in data integration and interpretation

It is actually very difficult to integrate different types of data, such as transcriptome, epigenome, and proteome data. The cotton genome is very complex and polyploid, and the large amount of data puts a lot of pressure on subsequent comparison, analysis, and understanding. We now need more powerful computational tools and unified analysis processes to process data from these different sources, resolve the contradictions between them, and finally extract meaningful biological information from them (Wang et al., 2020; Prasad et al., 2022).

8 Future Directions and Technological Advances

8.1 Single-cell omics for precise mapping of regulatory states during fiber development

In fact, it is not that no one doubts the existence of many regulatory processes, but the previous technology was too crude to grasp such a fine level. Now it is different. The emergence of single-cell omics has finally broken the fuzziness of "average value". It can directly depict the true picture of gene expression and epigenetic state at the level of a single cell-even the switching between different developmental stages can be distinguished in detail (Wang et al., 2020; Bai and Scheffler, 2024). In the past, the data given by mixed samples were too "fuzzy" to see which type of cells played a leading role. These new technologies solve the problems of "not being able to locate" and "not being able to see the details". Especially when single-cell transcriptome and spatial genomic data are combined, those regulatory factors "where they work and when they start to take charge" can finally be seen at a glance. This is of great significance for combing the regulatory chain of the entire cotton fiber development.

8.2 CRISPR-based functional validation of candidate regulatory elements

Not all candidate genes are worth further study, and not every regulatory region is really useful. This is when CRISPR comes in handy. Tools such as CRISPR/Cas9 and base editors are now used very skillfully in cotton research (Zhu and Luo, 2024). But don't get me wrong, the goal of these editing tools is not to "improve traits" immediately, but to verify. Whether the suspicious objects screened out by omics are the "key players" in regulating fiber development, using CRISPR to knock it out or overexpress it will quickly show changes. This is what Wen et al. (2023) did. Its significance is more than just verification. Once these direct evidences are available, the subsequent breeding direction will be clearer. Especially when breeding cotton varieties with better fiber quality, CRISPR can help you avoid detours and screen faster.

8.3 Machine learning for predictive modeling of gene regulatory networks

Not all candidate genes are worth further study, and not every regulatory region is really useful. This is when CRISPR comes in handy. Tools such as CRISPR/Cas9 and base editors are now used very skillfully in cotton research. But don't get me wrong, the goal of these editing tools is not to "improve traits" immediately, but to verify. Whether the suspicious objects screened out by omics are the "key players" in regulating fiber development, using CRISPR to knock it out or overexpress it will quickly show changes. This is what Wen et al. (2023) did. Its significance is more than just verification. Once these direct evidences are available, the subsequent breeding direction will be clearer. Especially when breeding cotton varieties with better fiber quality, CRISPR can help you avoid detours and screen faster.

9 Concluding Remarks

It's not that no one has paid attention to how cotton fiber develops, but in the early years, the tools and data were not detailed enough. In recent years, the development of transcriptomics and epigenomics has indeed allowed researchers to see deeper. From the transcriptome data, we can see which genes are active in the stages of initiation, elongation and maturity; and the research at the epigenetic level has gradually revealed how chromatin "controls" these expression rhythms.

Of course, these two methods have limited effects when used alone. What can really break down complex problems is to look at them together. Through integrated analysis, we can not only identify the key genes that

affect fiber quality and yield, but also draw a "blueprint" of the regulatory network, knowing who is in front, who is behind, who is leading, and who cooperates.

However, this alone is not enough. Understanding the mechanism is one thing, and whether it can be used in actual breeding is another. Therefore, the current research trend is more inclined to integrate the transcriptome, epigenome, and genome data together. Once the "components" such as QTL, regulatory factors, and expression modules are clearly disassembled, combined with molecular markers and algorithm models, we can have a more specific grasp of the entire development process.

In fact, breeding has long begun to try to "rely on molecular technology". Now there are a number of stable QTLs, candidate genes, and superior alleles that can be used, and marker-assisted selection is also in use. New research is still in progress, such as trying to further improve the length and strength of fibers by accumulating superior alleles and then using genomic tools. This road is not easy, but it is becoming clearer and clearer. The more mature the technology and the more integrated the data, the more likely it is that new cotton varieties with high quality and high yield will be bred.

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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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