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Epigenetic Regulatory Mechanisms Underlying Heat Tolerance in *Grapevine*

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Abstract This study summarizes the epigenetic regulatory mechanisms of grapes under high-temperature stress and discusses the application prospects of CRISPR/dCas9 epigenetic editing, epigenetic marker-assisted breeding, and stress memory in enhancing the stress resistance of grapes. Studies have shown that DNA methylation plays an important role in high-temperature responses. DNA methylation changes regulated by methylase can affect the expression of heat stress-related genes. Reversible regulation of histone modification can also alter the expression levels of heat shock proteins and transcription factors, thereby helping plants adapt to high temperatures. Some mirnas participate in the formation of heat tolerance in grapes by acting on transcription factors and regulating hormone signaling pathways. There exists a complex interaction network among methylation, transcription and protein levels, and genes such as *HSFA2* and *MBF1c* play important roles in this process. This study aims to provide theoretical support and technical references for molecular breeding of heat-tolerant grape varieties and cultivation management in response to climate change.

Keywords Grapevine (*Vitis vinifera*); Heat tolerance; Epigenetic regulation; DNA methylation; Non-coding RNA

1 Introduction

Global warming has made extreme hot weather common, which has a significant impact on the growth, development and fruit quality of economic crops like grapes (Li, 2024). High temperatures can inhibit photosynthesis in grapes, damage leaf structure and stomatal regulation, cause flower organ shedding, hinder fruit development, reduce sugar accumulation, resulting in decreased yield and poor quality (Venios et al., 2020; VanderWeide et al., 2022; Sun et al., 2025). Heat stress can also cause cell membrane damage, reactive oxygen species (ROS) accumulation, protein denaturation and metabolic disorders, disrupting the balance within plants (Liu et al., 2022; Chen et al., 2023). The tolerance to high temperatures varies greatly among different grape varieties and wild species. Heat-resistant varieties can maintain better photosystem II (PSII) function and have stronger antioxidant capacity (Nogales et al., 2020; Zha et al., 2020; Guo et al., 2025).

In recent years, the role of epigenetic regulation in plants' responses to stress such as high temperature, drought and salinity has been increasingly valued. Epigenetic regulation mainly includes DNA methylation, histone modification and regulation of non-coding RNA. These processes can affect gene expression and help plants adapt rapidly to the external environment (Sun, 2025). In grapes, Tan et al. (2023) and Zhang et al. (2023) found that miRNA-mediated mRNA degradation, DNA methylation, and histone modification are all crucial in response to high temperatures. These mechanisms help plants withstand high temperatures in the short term and may also affect the adaptability of offspring through "stress memory", providing a new direction for heat-tolerant breeding (Akhter et al., 2021).

This study summarizes the epigenetic regulatory mechanisms in the formation of heat tolerance in grapes, with a focus on the roles and network relationships of miRNA, DNA methylation, and histone modification in the high-temperature response. By integrating the research results of multiple omics and functional verification, this study reveals the core regulatory factors and molecular pathways of grape heat tolerance formation, aiming to provide a theoretical basis and practical reference for the molecular breeding and climate-adaptive cultivation of heat-tolerant grape varieties.

2 Heat Stress Responses in Grapevine: Physiological and Molecular Overview

2.1 Physiological responses: leaf temperature control, antioxidant systems, and photosynthetic adaptation

The leaves of grapes control leaf temperature by regulating the opening and closing of stomata and transpiration. Some heat-resistant varieties can still maintain a high stomatal conductance at high temperatures and reduce leaf temperature by enhancing transpiration cooling, thereby alleviating heat damage (Tan et al., 2023; De Oliveira et al., 2024). Grapes activate the antioxidant defense system and enhance the activities of enzymes such as superoxide dismutase (SOD) and catalase (CAT) to eliminate reactive oxygen species (ROS) produced under heat stress and protect cell membranes and protein structures (Ye et al., 2020; Zhen et al., 2023). In terms of photosynthesis, high temperatures can reduce the photosynthetic rate, with the most significant impact on photosystem II (PSII), leading to a decrease in chlorophyll content and obstruction of electron transfer. Heat-resistant varieties can usually reduce the damage of high temperature to the photosystem by enhancing mechanisms such as non-photochemical quenching (NPQ) and circulating electron flow (CEF), thereby maintaining a high photosynthetic efficiency (Guo et al., 2022; Qiu et al., 2025; Rodrigues et al., 2025).

2.2 Molecular responses: activation of heat shock proteins (HSPs) and transcriptional regulators

At the molecular level, heat shock proteins (HSPs) and heat shock transcription factors (HSFs) are the key regulatory elements for grapes in response to high temperatures. HSPs can help damaged proteins restore normal folding, prevent incorrect aggregation, and maintain intracellular protein stability (Figure 1) (Venios et al., 2020; Boopathy et al., 2022). HSFs are responsible for sensing thermal signals and initiating the transcription of stress genes such as HSPs. Studies have found that under high-temperature conditions, the expressions of genes such as *HSFA2*, *HSFA7* and *HSFB1* are significantly upregulated, and their expression levels are higher in heat-tolerant varieties (Ye et al., 2020; Zha et al., 2020; Chen et al., 2023). In addition, non-coding RNAs such as miRNA can also form more complex regulatory networks by regulating the expression of these heat-responsive genes (Ferrandino et al., 2023; Zhang et al., 2023).

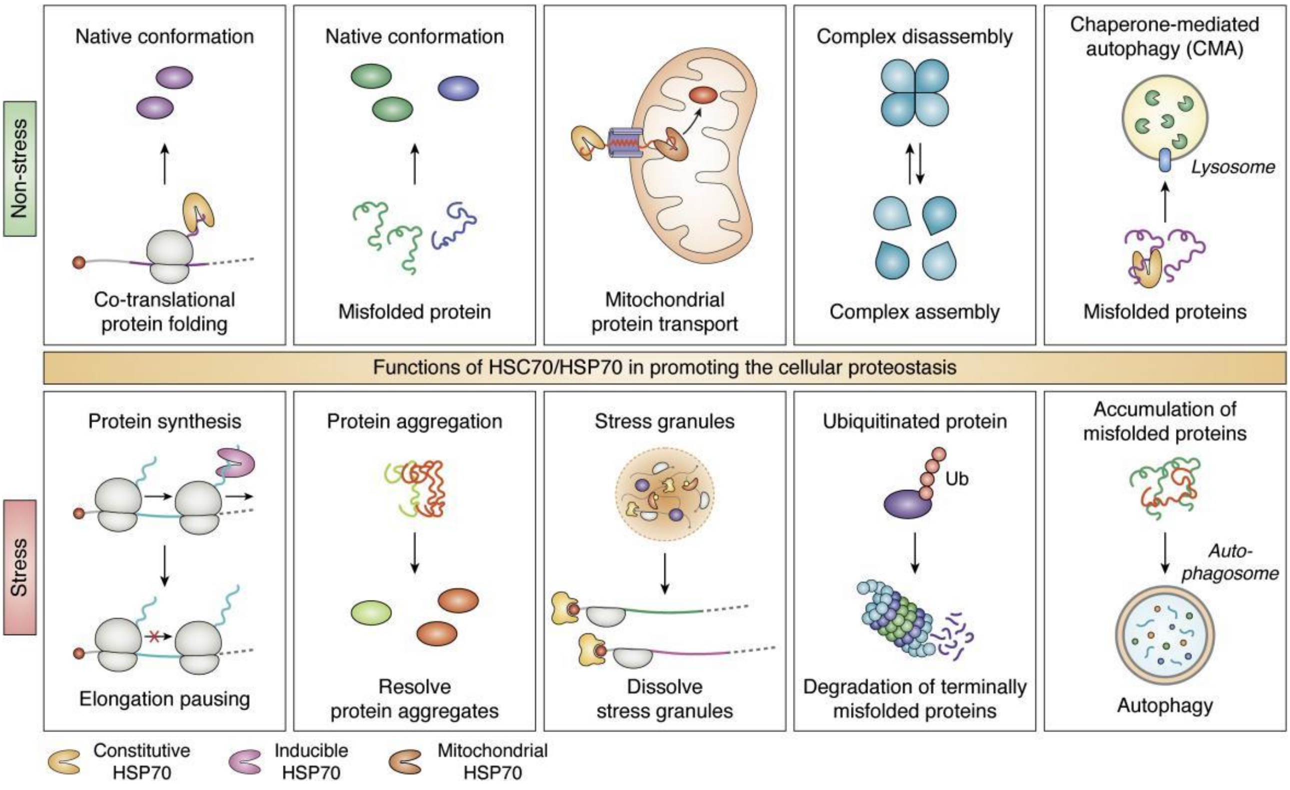

Figure 1 The function of HSC70/HSP70 in retaining the cellular proteostasis (Adopted from Boopathy et al., 2022)

2.3 Integration of stress signaling and gene expression reprogramming

Grapes do not rely on a single pathway to respond to heat stress, but integrate multiple signaling systems including hormone signals, calcium ion signals, and ROS signals. High temperature can induce the activation of the abolic acid (ABA) signaling pathway, helping plants regulate stomatal opening and closing and initiate the expression of stress resistance genes (Zha et al., 2020; Guo et al., 2022). Heat stress interacts with other environmental factors such as drought or UV-B radiation. Relevant transcription factors jointly regulate downstream genes and enhance overall stress resistance (Ju et al., 2021; De Oliveira et al., 2024). Molecular mechanisms such as epigenetic modifications and alternative splicing dynamically regulate gene expression, enabling grapes to have stronger adaptability at high temperatures (Tan et al., 2023; Ferrandino et al., 2023).

3 DNA Methylation and Gene Expression in Heat Tolerance

3.1 Patterns of DNA methylation under high temperature conditions

High temperatures can cause changes in the DNA methylation patterns of plants. The DNA methylation level of grapes, a perennial plant, shows a certain degree of plasticity in different environments. Research has found that when grapes grow in different regions, there are significant differences in the level of 5-methylcytosine (5-mC) in their DNA. When these plants were transplanted into the same environment, this difference would gradually decrease, indicating that DNA methylation is reversible and can also reflect environmental adaptability (Varela et al., 2024). In addition, heat treatment (such as in vitro hyperthermia) can also induce new methylation changes in grape cells, generally manifested as a decrease in the methylation degree of the CCGG site. In other plants, high temperatures sometimes increase genomic methylation and sometimes decrease it, depending on species, genotype and stress intensity (Zhao et al., 2020; Akhter et al., 2021). These changes mostly occur in the promoter region or the genome region, thereby affecting the gene expression related to stress response (Korotko et al., 2021).

3.2 Role of DNA methyltransferases (MET1, CMT3, DRM2) in stress memory and tolerance

Members of the DNA methyltransferase family, such as MET1, CMT3 and DRM2, play a key role in maintaining and reshaping DNA methylation. They are also related to the "stress memory" and heat tolerance of plants. Research has found that the natural variations of CMT2 and CMT3 are closely related to the CHH/CHG methylation pattern and temperature adaptability. Mutants lacking the cmt2 or cmt3 genes exhibit better heat resistance at high temperatures instead (Liu and He, 2020; Zhao et al., 2020; Sun et al., 2022). DRM2 regulates genomic methylation through the RNA-mediated DNA methylation pathway (RdDM), and its expression increases at high temperatures, enhancing genomic methylation levels (Akhter et al., 2021). MET1 is responsible for maintaining methylation at the CG site, and its activity is also affected by high temperatures. These enzymes work together, not only regulating gene expression, but also possibly passing on heat stress information to offspring through "epigenetic memory" to enhance their adaptability.

3.3 Correlation between methylation dynamics and transcriptional reprogramming in grapevine tissues

The dynamic changes of DNA methylation are closely related to the transcriptional regulation of grapes at high temperatures. High temperature can change the promoter methylation levels of some genes related to signal transduction, energy metabolism and stress response, thereby regulating their expression. Generally speaking, decreased methylation often leads to the upregulation of heat response genes (such as heat shock proteins or transcription factors), while elevated methylation inhibits the expression of some genes (Korotko et al., 2021; Varela et al., 2024; Yang et al., 2025). Some methylation changes can still be retained after environmental recovery, forming "epigenetic memory", which helps plants respond more quickly when exposed to high temperatures again (Liu and He, 2020; Zhao et al., 2020). Therefore, DNA methylation not only participates in the regulation of gene expression, but also supports the formation of heat tolerance in grapes at high temperatures through dynamic regulation and memory mechanisms.

4 Histone Modifications and Chromatin Remodeling

4.1 Key histone marks (H3K4me3, H3K9ac, H3K27me3) associated with heat-responsive genes

H3K4me3 and H3K9ac are usually associated with gene activation. Under heat stress, these two modifications will significantly increase in the promoter regions of heat shock protein (HSP) and heat response factor (such as Hsf) genes, thereby promoting the expression of these genes. For instance, in corn and Arabidopsis thaliana, heat stress can increase the levels of H3K4me3 and H3K9ac, and this change is closely related to the upregulation of heat response genes such as Hsf and rRNA (Hou et al., 2019; Wang et al., 2024). On the contrary, H3K27me3 is an inhibitory modification. Under heat stress, the demethylation of this marker can relieve gene suppression and help activate related genes (Yamaguchi and Ito, 2021; Zhu et al., 2023). In perennial plants such as grapes, the dynamic changes of histone methylation and acetylation are regarded as important molecular basis for the formation of heat stress memory and the establishment of heat tolerance (Tan et al., 2023).

4.2 Role of histone acetyltransferases (HATs) and deacetylases (HDACs) in transcriptional regulation

Histone acetyltransferases (HATs) can add acetyl groups at specific sites of H3 and H4 (such as H3K9, H3K14, H4K5), thereby weakening the binding between histones and DNA, making the chromatin structure looser, facilitating the binding of transcription factors and initiating gene expression. Heat stress can induce an increase in the expression of HAT genes and enhance the levels of active markers such as H3K9ac, thereby maintaining the sustained high expression of heat response genes (Wang et al., 2024). However, deacetylases (HDACs) have the opposite effect. They remove acetyl groups, making chromatin tighter and thereby inhibiting transcription. HDACs can also interact with proteins such as histone methyltransferase to regulate the interaction among various epigenetic markers, further influencing the gene expression pattern under heat stress (Wang et al., 2024).

4.3 Chromatin accessibility and its influence on stress-induced gene activation

The openness of chromatin determines whether transcription factors can come into contact with target genes. High-temperature stress can cause the rearrangement of chromatin structure, making the heat-response gene regions more easily recognized and bound by transcription factors, thereby achieving rapid activation (Wang et al., 2024). High-throughput analysis indicates that thermal shock transcription factors (such as HSFA1) reposition some cis-regulatory elements at high temperatures, helping to open the chromatin regions of related genes and promote expression. Furthermore, heat stress can also affect the three-dimensional structure of chromatin, activate certain transposons and heterochromatin genes, thereby making the epigenetic regulation of heat response more complex (Sun et al., 2020).

5 Non-coding RNA-Mediated Epigenetic Regulation

5.1 MicroRNAs (miRNAs) regulating transcription factors and stress-response pathways

miRNAs have positive or negative effects on heat tolerance by targeting transcription factors or stress-responsive genes. Research has found that the expression of various miRNAs changes significantly under high-temperature stress in grapes. miR167 can down-regulate the expression of its target genes ARF6 and ARF8, enhancing the heat tolerance of grapes. Heterologous expression experiments also verified the positive regulatory effect of miR167 (Ding et al., 2020; Islam et al., 2023; Zhang et al., 2023). The expression of miR3633a decreased at high temperatures, and its target genes *Vv-Atg36* and *Vv-GA3ox2* were upregulated. Overexpression of miR3633a can weaken the heat tolerance of grapes and affect the synthesis of oxidase and the expression of heat shock proteins. miR166 and miR393 are involved in the adaptation of grapes to high temperature by regulating transcription factors related to hormone signaling or cell wall metabolism (Campos et al., 2023).

5.2 Long non-coding RNAs (lncRNAs) as scaffolds for chromatin modification complexes

lncRNAs can affect the expression of stress response genes in a cis or trans manner. Some lncRNAs can also act as scaffolds for chromatin modification complexes (such as PRC2), mediating histone methylation or chromatin remodeling, and regulating the expression of downstream genes (Wu et al., 2020; Imaduwage and Hewadikaram, 2024). In grapes, a large number of lncRNAs show dynamic expression changes under cold stress and target stress-related transcription factors such as WRKY, Hsf, and NAC (Wang et al., 2019). Although current research on heat stress is still limited, it is speculated that they also have similar functions in heat regulation. In other plants such as poplar, some lncRNAs can bind to PRC2 complexes to form stable inhibitory chromatin structures and regulate the expression of heat-sensitive genes such as heat shock proteins (Chen et al., 2021).

5.3 Small interfering RNAs (siRNAs) in directing DNA methylation and gene silencing under heat stress

siRNAs can guide DNA methyltransferases to add methyl groups at specific sites to achieve gene silencing and transposon inhibition (Puchta-Jasińska et al., 2025). In plants, 24-nt siRNAs can move between different tissues, regulate genome-wide DNA methylation levels, maintain genomic stability, and affect the expression of stress response genes (Schwartz et al., 2020; Chow and Mosher, 2023). The siRNA-AGO4 complex can attract RNA polymerase V to new target sites, thereby initiating the RdDM cycle and establishing a new epigenetic silencing state (Sigman et al., 2021). Furthermore, siRNAs are also involved in the establishment and maintenance of stress memory, which is helpful for plants to respond more quickly when exposed to high temperatures again (Puchta-Jasińska et al., 2025).

6 Integrative Multi-Omics Insights into Epigenetic Regulation

6.1 Combining methylome, transcriptome, and proteome analyses for heat tolerance studies

Joint transcriptomic and proteomic analysis revealed that approximately 70% of genes in grapes underwent alternative splicing at high temperatures, with a significant increase in intron retention (IR) events, indicating that alternative splicing plays a crucial role in the heat tolerance response of grape leaves. Proteomic data further indicate that RNA-binding proteins (such as SR45, SR30, SR34) and ribonucleoprotein U1A are expressed at elevated temperatures, promoting the occurrence of these alternative splicing events. Heat shock proteins (HSPs) and key transcription factors (such as MBF1c, HSFA2) are upregulated at both the transcriptional and translational levels and jointly participate in heat regulation (Figure 2) (Liu et al., 2022; Chen et al., 2023; Tan et al., 2023).

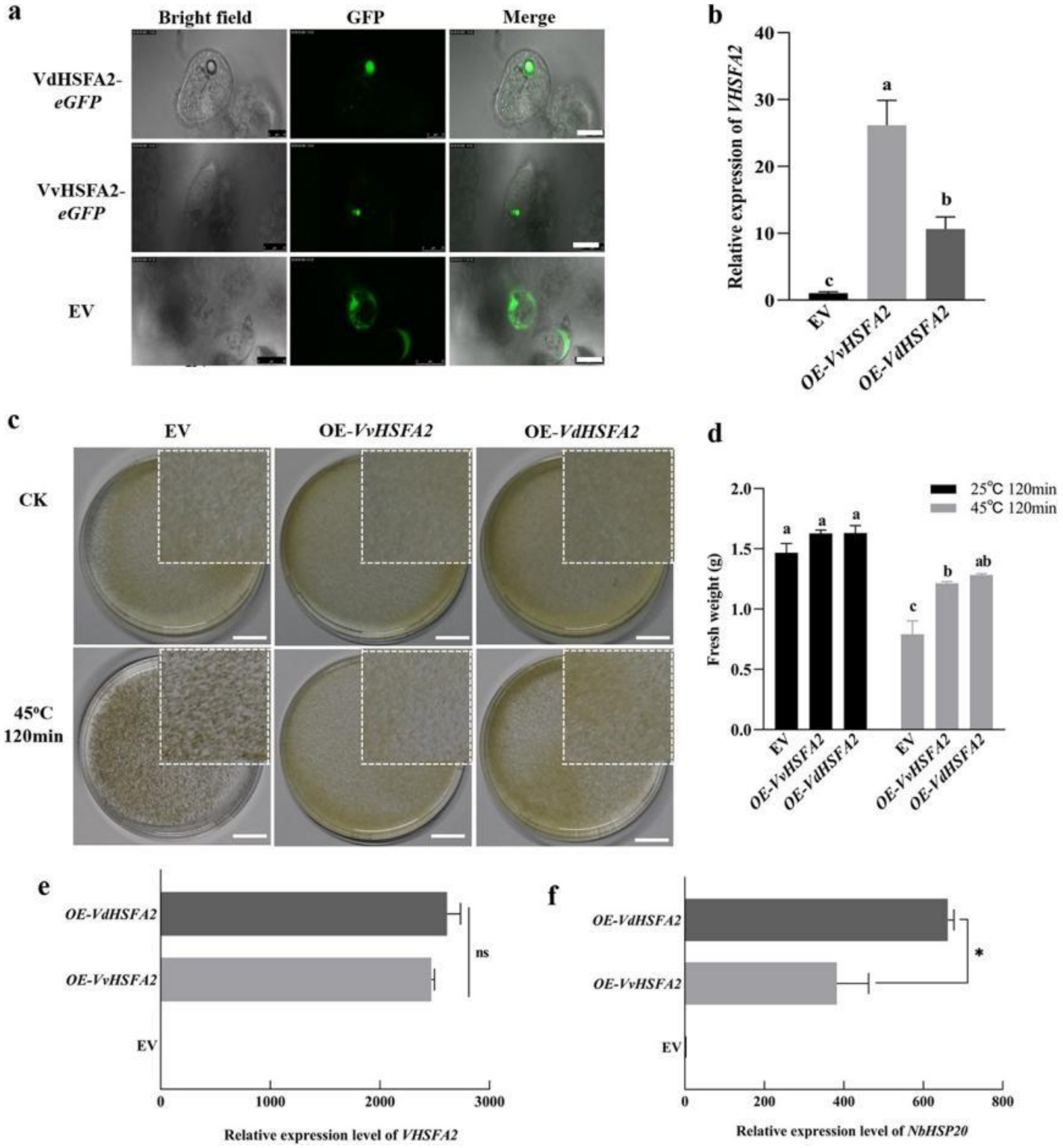

Figure 2 Overexpression of *VvHSFA2* and *VdHSFA2* improved heat tolerance in grape (Adopted from Liu et al., 2022)

6.2 Network analysis of epigenetically regulated heat-responsive genes

Researchers identified multiple gene modules significantly associated with heat tolerance through co-expression network analysis (WGCNA) of transcriptome data. These modules are enriched with functions such as fatty acid metabolism, starch and sucrose metabolism, plant hormone signaling pathways, and MAPK signaling pathways. Network analysis also found that some hub genes (such as *VIT_04s0044g01430*, *VIT_17s0000g09190*) are closely related to heat resistance. Among these modules, histone modify-related genes (such as histone lysine methyltransferase *SUVR3*) are located at the core position, indicating that epigenetic modifications play a key role in regulating the expression of heat-resistant genes (Liu et al., 2022; Tan et al., 2023; Wu et al., 2023).

6.3 Identification of key molecular hubs and signaling modules through systems biology

Systems biology studies combined with ChIP-Seq and RNA-Seq analyses further revealed that in heat-tolerant grape varieties (such as *Vitis davidii*), HSFA2 can directly regulate hundreds of target genes, far more than in varieties with weaker heat tolerance. Core genes such as *HSFA2*, *MBF1c* and *SUVR3* play a central role in regulating pathways such as heat shock proteins, antioxidant enzymes and glucose metabolism. The miRNA omics results also showed that miR156, miR167 and miR3633a were involved in the formation of complex heat-resistant epigenetic regulatory networks by regulating hormone signaling, MAPK pathways and DNA repair processes (Liu et al., 2022; Wu et al., 2023; Zhang et al., 2023).

7 Case Study: Epigenetic Regulation of Heat Tolerance in Grapevine Cultivars

7.1 Study background: comparing heat-sensitive and heat-tolerant *Vitis vinifera* varieties

Grapes are important cash crops worldwide, but they are highly sensitive to high temperatures. Many main cultivated varieties from mild or cool regions have difficulty adapting to the increasingly severe heat stress. In contrast, some wild species such as *Vitis davidii* have stronger heat tolerance, which is related to their long-term growth in high-temperature and high-humidity environments. Research has found that there are significant differences in heat resistance among different varieties. For instance, the physiological responses and gene expressions of the heat-tolerant variety ‘Tangwei’ and the heat-sensitive variety ‘Jingxiu’ at high temperatures are completely different (Liu et al., 2022; Chen et al., 2023; Wu et al., 2023). Therefore, a systematic comparison of the epigenetic regulatory mechanisms of these two types of varieties is helpful in revealing the molecular basis of grape heat tolerance and also provides a reference for breeding new heat-tolerant varieties.

7.2 Experimental design: genome-wide DNA methylation and transcriptome profiling under heat stress

In the research, heat-tolerant types (such as *V. davidii* ‘Tangwei’) and heat-sensitive types (such as *V. vinifera* ‘Jingxiu’) grapes are usually selected as materials and treated under normal temperature (25°C) and high temperature (40°C to 47°C) conditions. Subsequently, whole-genome DNA methylation omics (WGBS) and transcriptome (RNA-seq) analyses were conducted using high-throughput sequencing technology to compare the dynamic changes of gene expression differences, transcription factors, heat shock proteins (HSPs), and small Rnas (such as mirnas) between the two types under heat stress (Chen et al., 2023; Zhang et al., 2023). Some studies also integrated proteomic, metabolomic and histone modification data to reveal the regulatory network of heat resistance formation from multiple levels (Liu et al., 2022; Wu et al., 2023).

7.3 Key findings: epigenetic markers linked to sustained gene expression and thermotolerance

The results indicated that heat-tolerant varieties exhibited more differentially expressed genes at high temperatures. Key heat shock transcription factors (such as HSFA2, HSFB1) and their target genes (such as *MBF1c*) were expressed higher in these varieties, promoting the formation of heat-tolerant responses. Meanwhile, the promoter region of the HSF gene contains more cis-acting elements, which enables it to have higher transcriptional activity at high temperatures (Liu et al., 2022; Chen et al., 2023). Mirnas such as vvi-miR167 and vvi-miR3633a show significant changes in expression under heat stress, regulating the corresponding target genes and thus participating in heat tolerance regulation (Zhang et al., 2023). Among heat-resistant varieties, some genes (such as *VIT_04s0044g01430*) are continuously highly expressed and play a positive regulatory role; Some genes are highly expressed in heat-sensitive varieties and may play a negative regulatory role (Wu et al., 2023). In addition, epigenetic mechanisms such as DNA methylation, histone modification, and alternative splicing are also jointly involved in the heat stress response, regulating the expression and function of heat-heat-related genes (Liu et al., 2022; Tan et al., 2023).

8 Breeding and Biotechnological Implications

8.1 Utilizing epigenetic markers in molecular breeding for heat-tolerant grapevines

Epigenetic markers have great potential in the molecular breeding of heat-tolerant traits in grapes. Research has found that heat-tolerant and heat-sensitive grapes exhibit different epigenetic regulatory patterns at high temperatures. These differences involve the expression changes of key transcription factors (such as HSFA2, HSFB1) and stress-related genes, and can be used as molecular markers for screening heat-resistant varieties (Liu et al., 2022; Chen et al., 2023; Wu et al., 2023). The high-variation regions and SSR loci of the chloroplast genome can also provide a basis for the development of DNA molecular markers, thereby assisting in the selection of heat-tolerant traits. The epigenetic diversity and “memory effect” of grapes are particularly important, especially for asexual perennial crops, which are helpful for plants to adapt to the environment more quickly in climate change (Berger et al., 2023).

8.2 Potential of epigenome editing (CRISPR/dCas9-based systems) in modifying stress response genes

Epigenomic editing technologies such as CRISPR/dCas9 have opened up new paths for the precise regulation of heat-resistant genes. By binding dCas9 to epigenetic proteins such as DNA methyltransferase or demethylase, site-specific methylation or demethylation of the promoter region of the target gene can be achieved, thereby up-regulating or down-regulating the expression of related genes (Moradpour and Abdulah, 2019; Jogam et al., 2022). At present, studies have achieved DNA-free residue-free CRISPR/Cas9 editing and efficient CRISPR/Cas12a systems in grapes, providing a technical basis for future epigenomic editing (Najafi et al., 2022; Ren et al., 2023). These methods can not only be used for functional gene research, but also for the breeding of heat-tolerant varieties, and are expected to circumvent the regulatory restrictions of traditional genetically modified crops (Seem et al., 2024).

8.3 Long-term stress memory and heritable epigenetic adaptation in grapevine improvement

Grapes, as perennial woody plants, can form and maintain long-term stress memories. Studies have shown that grapes pretreated with high temperature or drought respond faster and have stronger resistance to re-stress, which is closely related to DNA methylation, histone modification and transcriptional regulation. Some epigenetic changes can also be inherited in asexual reproduction and become an important basis for grapes to adapt to environmental changes (Berger et al., 2023). This kind of memory is not only reflected in the “pre-activation” state of gene expression, but also related to mechanisms such as enhanced antioxidant activity and regulation of hormone signals. In the future, in-depth research on these heritable epigenetic regulatory mechanisms will provide new theoretical and technical support for the improvement of heat-tolerant traits in grapes and climate-adaptive breeding.

9 Challenges and Future Directions

9.1 Technical limitations in high-resolution epigenome mapping for perennial crops

Although epigenetics shows great potential in revealing the heat stress adaptation mechanisms of perennial crops such as grapes, high-resolution epigenomic research still faces many technical challenges at present. Compared with annual model plants, studies on the epigenetic dynamics of perennial woody plants such as grapes are still very limited. This is mainly due to factors such as the complex tissue structure of grapes, large sample differences, and long life cycle, which bring experimental difficulties. In addition, the content of polyphenols and polysaccharides in grape tissues is relatively high, which will affect the extraction efficiency of DNA and RNA, thereby limiting the application of cutting-edge technologies such as high-throughput sequencing and single-cell epigenomics (Berger et al., 2022). At present, the spatial and temporal resolution of the grape epigenome is still insufficient, making it difficult to precisely reveal the specific epigenetic regulation of different tissues or developmental stages (Berger et al., 2023; Venios et al., 2024).

9.2 Data integration challenges across omics platforms and environmental conditions

Multi-omics joint analysis (including genomics, transcriptomics, epigenomics and metabolomics, etc.) provides a more comprehensive perspective for understanding the heat tolerance of grapes, but there are still many challenges in data integration. The data types, sequencing depths and noise levels of different omics platforms vary greatly, resulting in high data heterogeneity and making it difficult to conduct unified analysis and result interpretation. In addition, the complex interaction between environmental factors (such as temperature, drought, ultraviolet rays, etc.) and genotypes also increases the difficulty of modeling and analysis. At present, multi-omics studies have mostly focused on a single stress factor, lacking systematic analysis of epigenetic networks under multiple stresses and in the field environment (Tello and Ibáñez, 2022; Venios et al., 2024). Although artificial intelligence and network analysis methods can help integrate data at different levels, they pose higher requirements for experimental design, data standardization and biological interpretation (Bodein et al., 2020; Cembrowska-Lech et al., 2023).

9.3 Future outlook: building an epigenetic database for grapevine stress resilience

To promote the further development of epigenetic research on grape heat tolerance, it is necessary to establish a unified and standardized epigenetic database. This database should integrate data from different omics, covering epigenetic modification information of multiple varieties, multiple environments and multiple developmental stages, and be associated with phenotypic, genotypic and environmental data. This can not only reveal the epigenetic regulatory network of grapes more systematically, but also provide theoretical and data support for epigenetic marker-assisted breeding and precision cultivation (Venios et al., 2024). In the future, combined with site-specific epigenetic editing technologies such as CRISPR and big data analysis, it is expected to accelerate the molecular improvement and wide application of complex traits such as heat tolerance in grapes (Berger et al., 2023; Tan and López, 2023).

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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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