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REVIEW ARTICLE

Epigenetics: an innovative lever for grapevine breeding in times of climatic changes

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ABSTRACT

Climate change imposes numerous threats to viticulture. Different strategies have been developed to mitigate these effects that range from innovative vineyard management methods and precision viticulture to the breeding of new varieties and rootstocks better adapted to environmental challenges. Epigenetics refer to heritable changes in genome functioning that are not mediated by DNA sequence variations. The recent discovery that epigenetic memories can mediate acclimation and adaptation of plants to their environment now provides new levers for plant improvement facing climate changes without significant impact on the genetic information. This can be mediated either by using the epigenetic memories of stresses and/or by creating epigenetic diversity in the form of new epialleles without changing the genetic information. Indeed, grapevine is a perennial grafted clonally propagated plant, and as such, presents epigenetic specificities. These specificities require adapting strategies that have already been developed in model plants but also offer opportunities to explore how epigenetic memories and diversity can be a major source of rapid adaptation to the environment for plants bearing similar properties. Among these strategies, both annual and trans-annual plant priming with different types of elicitors might provide efficient ways to better face (a)biotic stresses. The use of epigenetic exchanges between scion and rootstocks and/or the creation of non-targeted epigenetic variations at a genome-wide scale, or targeted using epigenetic editing, may provide innovative and promising avenues for grapevine improvement to face challenges imposed by climate changes.

KEYWORDS: epigenetic, climate change, DNA methylation, grapevine, histone post-translationnal modifications, plant memory

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INTRODUCTION

Current crop breeding relies entirely on genetic diversity, because change in deoxyribonucleic acid (DNA) sequences (mutations, allelic diversity) that affects traits of agronomic importance, can be identified from population or individual using appropriate sequencing-based and genetic methods. However, only a tiny fraction of the heritability of plant traits can be associated with genetic variations (Brachi *et al*., 2011), suggesting that DNA polymorphisms among the parents are not sufficient to explain the wide range of phenotypic variation observed and limiting our ability to improve the quantity and quality of crop production. This hidden heritability is particularly critical considering the current and future challenges in agriculture due to a rapid increase in global population and climate change that threaten food security. Furthermore, genetic diversity has been progressively reduced in many crops through selection schemes, as is the case for tomatoes (Lin *et al*., 2014) or when clonal propagation is the main route for plant multiplication as in grapevine (Verhoeven and Preite, 2014). In this context, epigenetic variations may provide an additional source of phenotypic diversity independently of DNA sequence changes. Understanding the contribution of epigenetic variation to the inheritance of traits of agronomic importance can potentially transform our current understanding of quantitative (epi)genetics and allows for the development of new tools for crop improvement (Bourrat *et al*., 2017). So far, the importance of plant phenotypic traits under epigenetic control is underestimated in crops, and the ability to use them in breeding schemes still needs to be implemented.

Epigenetics encompasses the complement of genetic information carried in chromatin beyond the DNA sequence. It includes DNA methylation which occurs on the 5th carbon of cytosine (5mC, Zhang *et al*., 2018) and on the 6th carbon of Adenine (6mA, Boulias and Greer, 2022), histone post-translational modifications (HPTMs), histone variants and chromatin remodelling (Lauria and Rossi, 2011). It can influence gene expression resulting in specific gene expression patterns during development and in response to stresses (Pikaard and Mittelsten Scheid, 2014). In plants, DNA methylation occurs at cytosines in the symmetrical CG and CHG and in the non-symmetrical CHH (H being A, T or C) sequence contexts (Zhang *et al*. 2018). In addition to methylome dynamics that take place during plant development, for example, during tomato fruit ripening (Zhong *et al*., 2013), changes in methylation patterns can be generated in response to environmental stresses (Furci *et al*., 2019), in part memorised and eventually transmitted to the following generations (Gallusci *et al*., 2022). Similarly, HPTM remodelling was described both during plant development and in response to abiotic and biotic stresses (Zhao *et al*., 2019). In addition, heritable DNA methylation variations, known as epi-alleles, affect agronomical relevant traits including sex determination in melon (Martin *et al*., 2009), rice height (Miura *et al*., 2009), yield in oil palm (Ong-Abdullah *et al*., 2015) and ripening in tomato (Manning *et al*., 2006), have been recurrently observed in plants.

As far as the grapevine is concerned, epigenetic studies are in their early stages (Gallusci *et al*., 2017). Yet the evidence is accumulating that epigenetic mechanisms are important for the development and responses to environmental challenges in grapevine (Table 1) as in many other plants (Pikaard and Mittelsten Scheid, 2014). In this review article, after a general description of the threats that climate changes impose on grapevines, we present the current knowledge concerning epigenetic studies in grapevines. We describe the plant epigenetic memories of stresses and discuss how these can be used as a new lever to improve grapevine tolerance to stresses. We also discuss ways to generate epigenetic diversity by exploiting the specificity of grapevine, a grafted, perennial clonally propagated, woody plant. We present innovative approaches to develop epi-breeding strategies in grapevine, which would allow one to directly use elite varieties to generate phenotypic diversity independently of sequence variations, thereby providing innovative and more rapid ways for grapevine improvement.

CHALLENGES OF CLIMATE CHANGE IN VITICULTURE

1. Climate change impacts on viticulture

Climate change is a major challenge in grape and wine production. The main consequences of climate change comprise global warming, modifications in rainfall timing and quantities, longer summers, enhanced climate variability (e.g., floods, droughts and heatwaves), the rise of the sea level, and increasing frequency and intensity of extreme climatic events such as hail storms and gale force winds, and in some regions hurricanes and an increase in various pathogen attacks (Figure 1). An increase in global average temperature (global warming) near the Earth's surface has been the most notable change over the last century. Temperature trends, focusing on viticulture regions, show that mean temperatures of the growing season have increased by about 1.3 °C from 1950 to 1999, and 1.7 °C from 1950 to 2004 in Europe (Fraga *et al*., 2012). Additionally, a 2 °C rise in average temperature is predicted for the next 50 years in wine-growing regions (Jones *et al*., 2005).

Additionally, consequences of global warming on viticulture include shorter growing seasons and early phenological stages such as earlier dates for bud break, flowering and fruit maturity (Fraga *et al*., 2016). The impact of climate change may differ depending on grapevine varieties and across viticulture regions. In some regions, predicted temperatures may increase over the optimum temperature thresholds of the currently cultivated varieties, which may result in an unbalanced maturity of berries and threaten the production of the current wine styles (Jones *et al*., 2005). In contrast, other less-known wine-pricing countries (England, Sweden, Denmark) that could not produce wines so far, may become well-known for wine production. Climate change may also affect the distribution of grapevine varieties within and between wine-growing areas (Abel and O'Neill, 2011). Finally, climate change-related factors likely to influence

grape production are the prevalence of various pests and diseases, as well as the vectors responsible for disease distribution (Van Niekerk *et al*., 2011).

2. Grape berry development and quality is affected by climate changes

Climate change results in multiple (a)biotic stresses that affect all aspects of plant development. Among those, alteration of yield (floral initiation, cluster number per bud, fruit set, berry size, (Keller, 2020), and of the berry ripening process (soluble solids, organic acids, phenolic compounds) affect wine quality and production, and have a profound economic impact on growers (Gutierrez Gamboa *et al.*, 2021). For example, an increase in sugar accumulation in berries associated with alterations in the balance between the different berry metabolites will result in shorter and earlier harvest periods (Bonada and Sadras, 2015). It will also shorten the time of harvest between cultivars which poses a challenge for viticulturists and agronomists to determine harvest time and logistics (Palliotti *et al*., 2014).

It is well described that high temperatures impact both, primary and secondary metabolism, eventually uncoupling the accumulation of sugars from anthocyanins during berry ripening. It leads to low anthocyanin content in berries at harvest, hence affecting the colour-alcohol balance of wines (Sadras and Monzon, 2006). An increase in temperature also results in berries with low titratable acidity, high pH and potassium accumulation. Low-acid grape juice requires the addition of tartaric acid to balance the high sugar level and enhance microbial stability, making the winemaking process costlier (Keller, 2020). Additional physiological disorders due to high temperatures and excessive solar radiation include berry dehydration and sunburn. Dehydration often results in berry shrivelling, which is strongly correlated to climate changes associated with low rainfall, long dry summers, and the occurrence of droughts and heatwaves (Zhang and Keller, 2015). It leads to an increase in berry sugar content, therefore to higher alcoholic levels in wines that may alter the inherent style of wines in some winegrowing regions (Santos *et al*., 2020). This has been well described for the late season dehydration phenomenon (LSD), as for Shiraz, which results in berries losing weight due to water loss (McCarthy and Coombe, 1999), and, as a consequence, an increase in sugar concentration. Berry sunburn occurs when grapes are exposed to high temperatures and ultraviolet radiation (Krasnow *et al.*, 2010), and may inhibit colour development, especially in grapevines cultivated in hot viticultural regions (Van Leeuwen and Darriet, 2016).

3. Facing climate change requires a diversity of strategies

Various strategies are being evaluated and some are already implemented around the world to limit the consequences of climate changes on viticulture. They include different culture management practises and long-term approaches, such as the breeding of new varieties (scion and rootstocks) better adapted to pathogens or more tolerant to abiotic stresses (Figure 1).

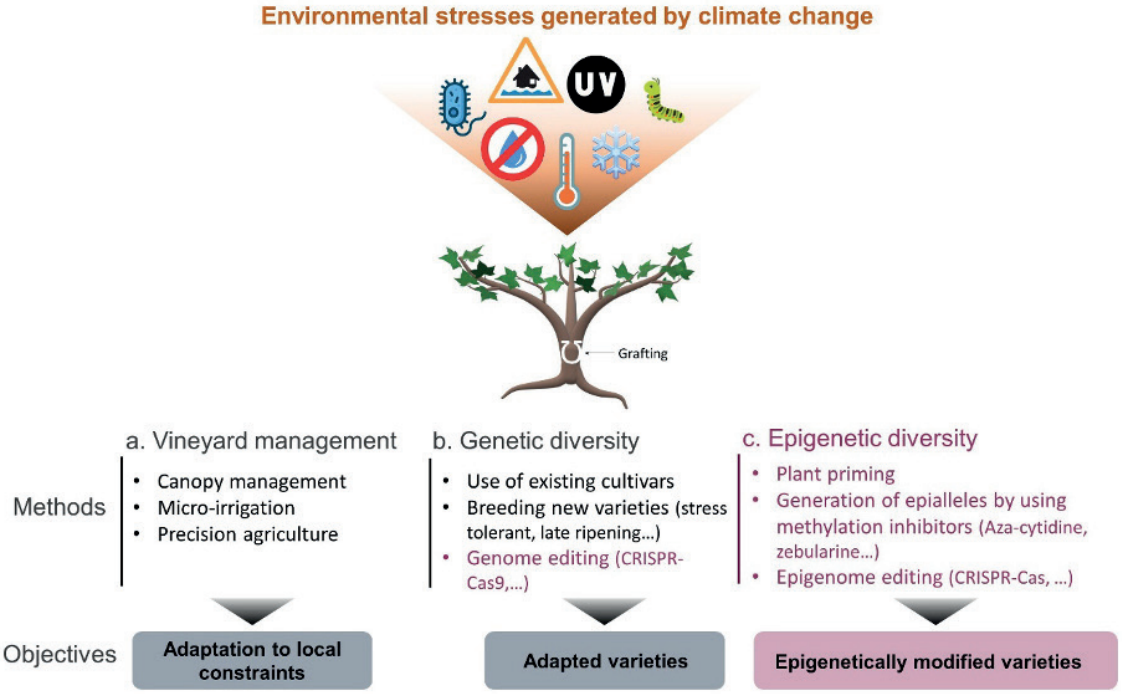


FIGURE 1. Possible strategies to tackle climate threats to grapevine.

Current strategies to face environmental challenges include innovative culture management (a), the use of already existing varieties and the breeding of new ones better adapted to pathogens or more tolerant to abiotic stresses or the use of genome editing to achieve the same goals (b). Epigenetic regulations and memories are essential processes involved in the acclimatisation and adaptation of plants to their environment and are likely critical in clonal populations with limited genetic diversity. Epigenetic regulations and diversity may be used as new levers for grapevine improvement to face environmental stresses. This includes plant priming and the generation of random, or targeted epigenetic changes to create epigenetic diversity (c).

The current strategies evaluated to mitigate the impacts of global warming on grape and wine quality can be grouped as follows: Pruning techniques; Canopy management; Reduction of radiation and temperature; and Irrigation management (Gutierrez-Gamboa *et al*., 2021).

In general, the purposes of these techniques are delaying the ripening period to allow the grapes to mature under cooler conditions and moderate temperatures, and decrease the incidence of some berry disorders. Changes in the traditional pruning techniques are being evaluated to delay phenology and alter sink to source ratio. Minimal pruning allows for increasing yield, reducing TSS, delaying fruit maturity, and producing must with better organic acid composition, greater wine colour and higher phenolics content than traditionally pruned grapevines (Zheng *et al*., 2017). Although less efficient, late pruning is another strategy used to delay phenology and ripening time (Morgani *et al.*, 2022).

Various canopy management techniques have been developed to alter source to sink ratio to obtain grapes with a suitable quality for wine production, characterized by a good metabolic balance, and lower soluble solids concentration. Among them, the most widely used and promising techniques are severe shoot trimming and leaf removal, which can be carried out mechanically and at different times of the annual vine growth cycle. In most cases, the reduction of sources (leaf area) and delayed harvest time resulted in the production of berries with decreased Total Soluble Solids and higher anthocyanin content (Martínez de Toda *et al*., 2017; Herrera *et al*., 2015).

Other strategies, such as antitranspirant sprays and shading nets are implemented to moderate temperatures and solar radiation of the cluster zone. The spray of kaolin-based sunscreens reduces the canopy temperature by 4 °C to 6 °C maintaining a high photosynthetic activity, preventing photoinhibition and avoiding physiological damage such as chlorotic and necrotic leaves, dehydrated berries and sunburn damage (Frioni *et al*., 2019). In the case of shading nets, while they can efficiently reduce radiation and temperature of leaves and fruits, they may have adverse effects on ripening and photosynthesis that require to be taken into account (Gutiérrez-Gamboa *et al.*, 2021).

Water availability is also becoming a major threat in viticulture, even more, challenging considering the drying trend predicted by climatic models. Therefore, producers have developed focused approaches to monitoring and regulating water use, such as the use of micro-sprinkler, dripper lines and partial root-zone drying. The recent development of precision viticulture may also alleviate the local effects of global warming and climate changes on grapevine plants.

Other practices applied from the establishment of the vineyard include a shift from low-density, high-yielding vines pruned and trained to replacement cane or cordon. The latter was replaced with plantings with different densities. Lyre, Smart-Dyson and ballerina trellis systems were applied to accommodate high vigour which translates to higher yields. The former trellis system also creates a cooler microclimate for the grapes to ripen. However, it may result in higher fungal disease pressure during a wet season (Reynolds and Vanden Heuvel, 2009).

Vineyard management will help mitigate the short-term effects of climate change on the grapevine. In the long term, using the already existing genetic diversity by planting cultivars known to be late ripening and/or drought resistant instead of the traditional varieties should also be considered. In addition, breeding which aims at generating new cultivars and rootstocks resistant to pests and/or better adapted to climate change could also provide long-term solutions. At present, new varieties resistant to downy mildew and powdery mildew have already been obtained, although their use remains limited due to the lack of acceptance of their wine quality (Töpfer and Trapp, 2022). The creation of varieties producing low-alcohol wines, or more tolerant to abiotic stresses is also currently being developed to mitigate the effect of climate change on wine quality. However, breeding new varieties remains a long and challenging work in grapevine (Töpfer and Trapp, 2022; Delrot *et al.*, 2020).

4. Epigenetics may provide new levers for grapevine adaptation to climate changes

In this context, strategies that could lead to plants better adapted to their environment without any changes to their genetic information could be advantageous as they may hasten the development of new plant lines while maintaining the currently used cultivars. Recently, epigenetic regulations and memories have emerged as essential processes involved in plant development and response to environmental stresses (Lämke and Bäurle, 2017) including in grapevine (Table 1).

This epigenetic information embodies an important part of the memory of cells and is likely playing an important role in the acclimatisation and adaptation of plants to their environment, even more importantly in clonal populations with limited genetic diversity such as grapevine. Using the epigenetic memory of plants may therefore provide innovative tools to better adapt currently used cultivars to their environment, in the absence of genetic variations. As will be discussed below, these approaches include priming plants with elicitors or moderate stresses, the creation of epigenetic diversity in clonal populations, or the creation of targeted and specific epigenomic changes (Figure 1).

EPIGENETIC MECHANISMS IN PLANTS: A SUMMARY

Epigenetic mechanisms include genomic DNA methylation which can occur on the 5th carbon of cytosine (5mC; Law and Jacobsen, 2010; Zhang *et al*., 2018) and on the 6th carbon of Adenine (6mA; Boulias and Greer, 2022). The latter has been recently identified in multicellular eukaryotes, and little is known about the mechanisms underlying 6mA regulation and roles in plant cells. *De novo* DNA methylation at cytosine is mediated by the RdDM pathway which involves the Domain Rearranged Methyltransferases 1, 2 (DRM1/2), DRD1 and 24nt-long

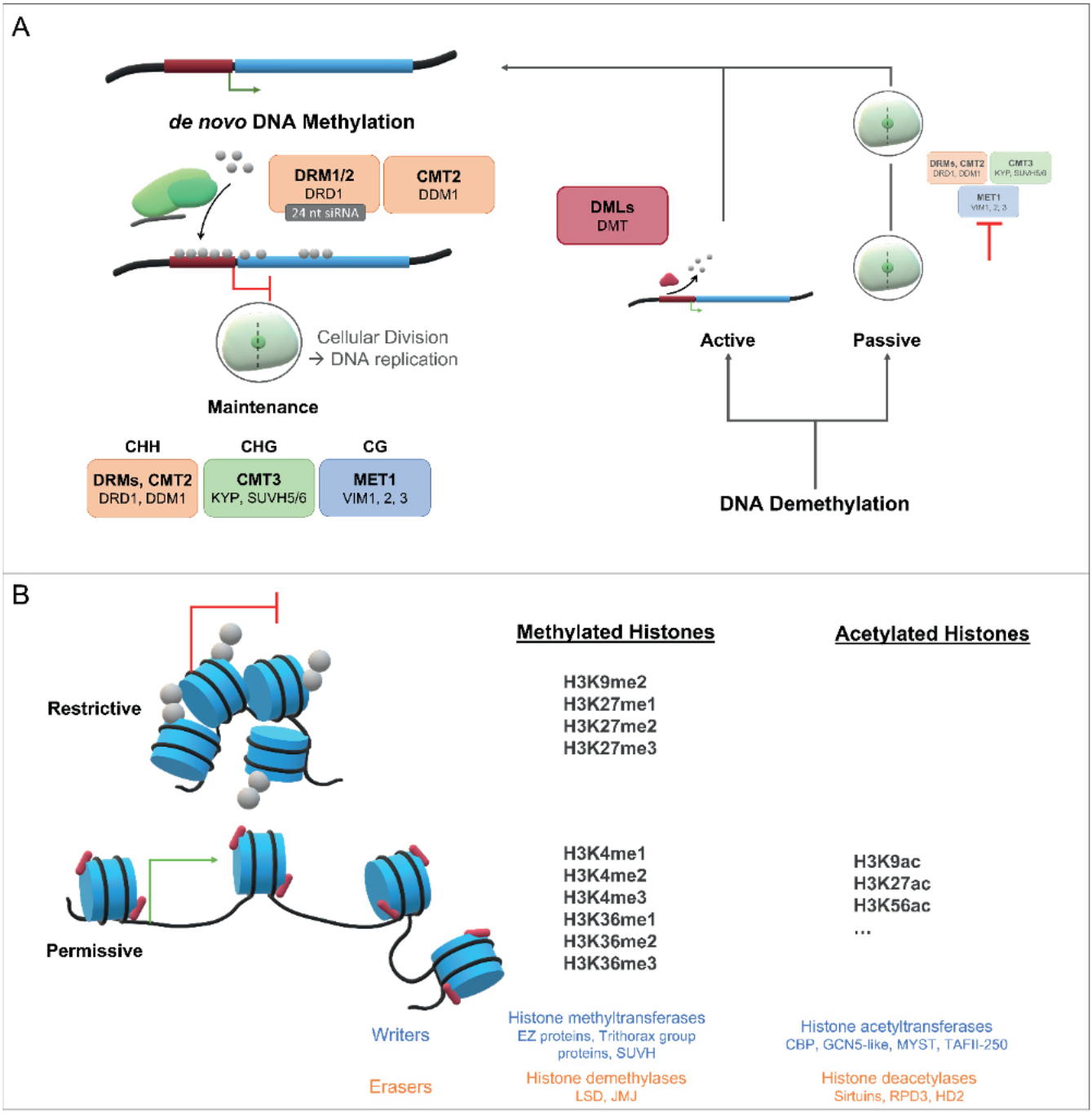


FIGURE 2. Epigenetic mechanisms in plants.

(A) *de novo* DNA methylation relies on the RNA-directed DNA methylation pathway (RdDM), which involves DRM1/2, small interfering RNAs (siRNAs) and scaffold RNAs in addition to an array of proteins. DNA methylation maintenance in both CG and CHG contexts are performed by MET1 and CMT3, CMT2, respectively. The maintenance of CHH methylation is carried out by the RdDM pathway and CMT2. DNA methylation can be passively lost after DNA replication in a non-targeted or actively removed by the DMTs enzymes that are targeted to specific loci. DNA methylation can impact gene expression by modulating chromatin accessibility to the transcriptional machinery when found in the promoter (coloured in red) and to a lesser extent within genes (coloured in blue).

(B) Histone H3 methylation and acetylation and associated chromatin states as examples of Histone H3 post-translational modifications. Methylated histones can either be found in transcription-restrictive or permissive chromatin, depending on the modified lysine residue position on the histone tail (Kx) and the number of methyl groups carried (me1, me2, me3). Acetylated histones are correlated with active gene expression. Only the most studied acetylation marks in plants are listed here. Different protein families are involved in the addition (writers, in blue) or the removal (erasers, in orange) of histone marks. Amino acids that are modified and their position are indicated. DRM1/2 (Domain Rearranged Methyltransferase ½), CMT2/3 (chromomethylase 2/3), MET1 (DNA methyltransferase 1), VIM1-3 (variant in methylation 1-3), KYP/SUVH4 [KYP/Su-(var)3-9 homolog 4], SUVH5/6 [Su-(var)3-9 homolog 5/6], DRD1 (Defective in RNA-directed DNA methylation), DDM1 (Decrease in DNA methylation) and 24nt siRNA (24 nucleotide small interfering RNAs), DML (DEMETER(DMT)-LIKE demethylase), E(Z) (Enhancer of Zeste proteins), KYP (KRYPTONITE), LSD (Lysine Specific Demethylases), JMJ (Jumonji-type histone demethylases), CBP (p300/CREB binding protein), GCN5 (General Control Non-derepressible protein 5), MYST (MOZ, Ybf2/Sas3, Sas2 and Tip60), TAF (TATA-binding protein (TBP)-associated factor, RPD3 (Reduced Potassium Deficiency 3).

small RNAs, and by the chromomethylase 2 (CMT2) with Decrease in DNA Methylation (DDM1) for CHH localized in heterochromatic regions (Zemach *et al*., 2013). After cell division, newly produced DNA is hemimethylated at CG and CHG symmetrical sites. Maintenance of methylation in the CG context relies on the activity of MET1 together with VIM1, 2 and 3. The CHG methylation maintenance depends mainly on the activity of CMT3. In the asymmetrical context of CHH, re-methylation of the newly synthesized DNA strands depends on both the RdDM pathway and CMT2 activity. CMTs are dependent on histone methylation mediated by KYP and SUVH5 and 6 (for a complete review of DNA methylation, Zhang *et al*., 2018). The 5mC can be actively removed by DNA glycosylase/lyase, also called DNA demethylases (DMT). DNA demethylation can also occur passively in a replication-dependent manner when the methylation machinery is not or poorly active after cell division (Liu and Lang, 2020; Figure 2A).

Epigenetics mechanisms also include histone variants and histone-post translational modifications (HPTMs) that mainly occur on lysine, threonine and serine residues within the histone amino-terminal tail. HPTMs include acetylation, methylation phosphorylation, ubiquitination, sumoylation and ADP ribosylation. Nucleosome composition and HPTMs can affect chromatin structure and directly determine the formation of a transcriptionally active or inactive state by modifying the interaction between DNA and nucleosomes (Lauria and Rossi, 2011). While histone acetylation localised within coding regions is associated with active transcription, histone methylation has been correlated to different types of effects on gene expression, depending both on the position of the lysine and on the number of methyls added (mono, di, tri-) (Figure 2B). Similar to DNA methylation, the addition and removal of histone marks are regulated by specific proteins respectively called writers (for example, Histone Methyltransferases/HMT, Histone Acetyltransferases (HATs) and erasers (Histone Demethylases/HDM, Histone Deacetylases/HDACs) (Figure 2B). The activity of enzymes involved in epigenome regulation relies on the availability of metabolic precursors and co-factors, that can be altered by environmental stresses (Leung and Gaudin, 2020).

EPIGENETICS IN GRAPEVINE: CURRENT STATE OF THE ART

Epigenetic mechanisms are involved in the regulation of many processes in grapevines, even though their study is still in its infancy in this plant (Table 1). Recent advances include the description of leaf and fruit methylomes that have brought light to the general distribution of methylated cytosine in the grapevine genome (Niederhuth *et al*., 2016; Williams *et al*., 2020). Results indicate that mCG and mCHG levels range between 45 % and 50 % and 31 to 35 %, respectively. Most remarkably, the level of CHH methylation is very low as compared to most plants, ranging between 1.1 and 4 %, which seems to be a characteristic of clonally propagated plants (reviewed Ibañez and Quadrana, 2022). Indeed, clonal propagation of grapevine is a widespread agronomic practice and it is unknown whether wild grapevine plants have a similar methylome signature and what functional consequences this unusual methylation pattern may have.

In addition, there is accumulating evidence of the role of epigenetic regulations in the development and ripening of grape berries, in the interaction between the grapevine plant and its environment and during the grafting process as explained below (Table 1).

1. Epigenetic regulation of grape berry development and ripening

Early epigenetic studies focused on the characterization of genes involved in the control of histone post-translational modifications in fruits. Hence, more than 30 grapevine genes encoding SET domain proteins and Polycomb Repressive Complex 2 (PRC2) components and genes coding for HAT (Histone Acetyl Transferases) have expression patterns that are consistent with a possible role of the corresponding proteins in grape berries (Aquea *et al*., 2010, 2011; Qian *et al*., 2015; Zhao *et al*., 2015). More recently, the description of grape berry methylomes has been performed. The results did not reveal major changes in DNA methylation levels or distribution (Shangguan *et al*., 2020). This is different from tomato, strawberry or orange fruits, which display major methylome remodelling at the ripening stage (for a review, Tang *et al*., 2020). In these three fruits, DNA (de)methylation plays a major role in fruit ripening control. This function was suggested to be ensured by the repressive histone mark H3K27me3 in grapevine as in many other fruits, suggesting a convergent fruit evolution (Lü *et al*., 2018). In grapevine leaves, the H3K27me3 marks are enriched at genes encoding transcription factors of the NAC and MADS-box family. In contrast, in grape berries, these genes were activated and the repressive H3K27me3 mark was removed, consistent with possible involvement in berry ripening control (Lü *et al*., 2018). However, the exact function of this repressive mark and of the targeted genes during berry ripening remains to be investigated. Interestingly, H3K27me3 seems also to control methoxypyrazine accumulation in grape berries by inhibiting the expression of the *VMOT3* gene in a cultivar-dependent way (Battilana *et al*., 2017).

2. Epigenetic regulations are involved in grapevine response to environmental stresses

Another important function of epigenetic regulations is to mediate and integrate plant responses to (a)biotic stresses making epigenetic mechanisms an important lever for plant adaptation to environmental challenges (Guarino *et al*., 2022). Consistently, genes involved in the regulation of HPTMs were differentially expressed when grapevine was subjected to combined heat and drought stress (López *et al*., n.d.), suggesting important remodelling of HPTM landscapes after these stresses. So far only a few epigenomic studies have been performed to evaluate grapevine response to (a) biotic stresses. Indeed, recent evidence suggests that DNA methylation levels vary in a cultivar-dependent manner in response to mildew infection (Azevedo *et al*., 2022).

TABLE 1. List of epigenetic studies performed in grapevine.

Research papers			
Experimental approaches	Themes	References	Epigenetic mechanisms
Analysis of epigenetic regulator encoding genes	PcG proteins	Almada *et al.* (2011)	HPTMs
	SET DOMAIN GROUP proteins	Aquea *et al.* (2011)	
	HAT	Aquea *et al.* (2010)	
	Sirtuins	Aquea *et al.* (2010); Cucurachi *et al.* (2012)	
	H3K4 methyltransferases	Shang *et al.* (2021)	
	proteins involved in the RdDM pathway	Xiang *et al.* (2022)	DNA methylation
	DNA methyltransferases	Heriberto *et al.* (2016)	
	Demeter-like proteins	Kiselev *et al.* (2013a); Xiang *et al.* (2022)	
Analysis of epigenetic marks/ effect of inhibitors of epigenetic mechanisms	Secondary metabolism	Kiselev *et al.* (2015)	DNA methylation
		Kiselev *et al.* (2013a); Kiselev *et al.* (2013b)	
		Xia *et al.* (2021)	
		Kong *et al.* (2022)	
	Development/phenology	Azuma and Kobayashi (2022)	DNA methylation
		Jia *et al.* (2020)	
		Guo *et al.* (2019); Jia *et al.* (2023)	
		Shangguan *et al.* (2020)	
		Rubio *et al.* (2022)	DNA methylation and HPTMs
		Lü *et al.* (2018)	
		Battilana *et al.* (2017)	HPTMs
		Cheng *et al.* (2022)	
		Jia *et al.* (2023)	
	Biotic stress response	Azevedo *et al.* (2022); Jia *et al.* (2023)	DNA methylation
		Gao *et al.* (2020)	
		Pagliarani *et al.* (2020a)	
		Pagliarani *et al.* (2020a); Pereira *et al.* (2022)	
		Peian *et al.* (2021)	HPTMs
	Abiotic stress response	Baránek *et al.* (2015); Peian *et al.* (2021)	
		Baránek *et al.* (2015); Marfil *et al.* (2019); Peian *et al.* (2021)	DNA methylation
		Bernardo *et al.* (2017)	
	Description, Comparison with other species	Niederhuth *et al.* (2016)	DNA methylation
		Magris *et al.* (2019); Niederhuth *et al.* (2016)	
		Bester *et al.* (2017)	Small RNAs
		Bester *et al.* (2017) ; Schwope *et al.* (2021)	Chromatin conformation
	Clonal variation	Varela *et al.* (2021)	DNA methylation
		Ocaña *et al.* (2013)	
		Williams *et al.* (2020)	
		Xie *et al.* (2017)	
		Imazio *et al.* (2002)	Small RNAs
		Paim Pinto *et al.* (2016)	
	Effect of in vitro culture and/or transgenesis	Schellenbaum *et al.* (2008)	DNA methylation
		Dal Santo *et al.* (2022); Schellenbaum *et al.* (2008)	
		Lizamore *et al.* (2021)	
		Dal Bosco *et al.* (2018)	
		Dal Bosco *et al.* (2018; Gambino *et al.* (2010)	
		Martínez *et al.* (2021)	HPTMs
		Atanassov *et al.* (2022)	
Methodology paper			
Hermawaty *et al.* (2022)			
Reviews			
Fabres *et al.* (2017)			
Fortes and Gallusci (2017)			
Kong *et al.* (2019)			

*References are indicated in the main reference list

In addition, DNA methylation remodelling at genes involved in photosynthesis and secondary metabolism was demonstrated in plants recovering from *Flavescence Dorée* infection. This suggests possible DNA-methylation mediated memory effects (Pagliarani *et al*., 2020a). In another study, the use of melatonin, a signal molecule that elicits a better response of grapevine to both biotic and abiotic stresses, was shown to lead to modified DNA methylation levels in grape berries in part associated with changes in gene expression (Gao *et al*., 2020).

More globally, environmental conditions were associated with changes in DNA methylation distribution. Comparing Malbec clones grown in vineyards with contrasted environmental conditions showed a correlation between epigenetic variations, phenotypic plasticity and clonal diversity (Varela *et al*., 2021). An epigenetic memory of abiotic stresses such as UV-B and drought was also suggested in the Malbec cv. after 1 year of treatment (Marfil *et al*., 2019).

3. Epigenetic dialogue during grafting.

Following the historical Phylloxera crisis at the end of the XIXth century, the grapevine species *Vitis vinifera* has been grafted in most vineyards in the world. Interestingly, the association between the scion and the rootstock can modify the scion phenotype, including its development, metabolism as well as its response to environmental stresses (Ollat *et al*., 2017). Although graft-dependent effects have been well described in many different species, the underlying mechanisms are not clearly understood. Interestingly, several reports suggest that epigenetic-based mechanisms participate in the rootstock-dependent modifications of the scion phenotype rootstock. Indeed, the comparison of scion methylome depending on the rootstock genotype demonstrates that the interaction between scion/rootstock impacts the epigenome of the scion, possibly with an effect on its phenotype (reviewed in Jeynes-Cupper and Catoni, 2023). Experiments using Arabidopsis mutants affected in their ability to produce small RNA were used to demonstrate that mobile small RNA are involved in *de novo* methylation in the scion and the rootstock (Jeynes-Cupper and Catoni, 2023). Although none of these epigenetic studies were conducted on grapevine, it has been already described that grafting grapevine induced phenotype and transcriptomic reprogramming (Cookson *et al*., 2013). Consistent with the role of epigenetics in this process, recent works have

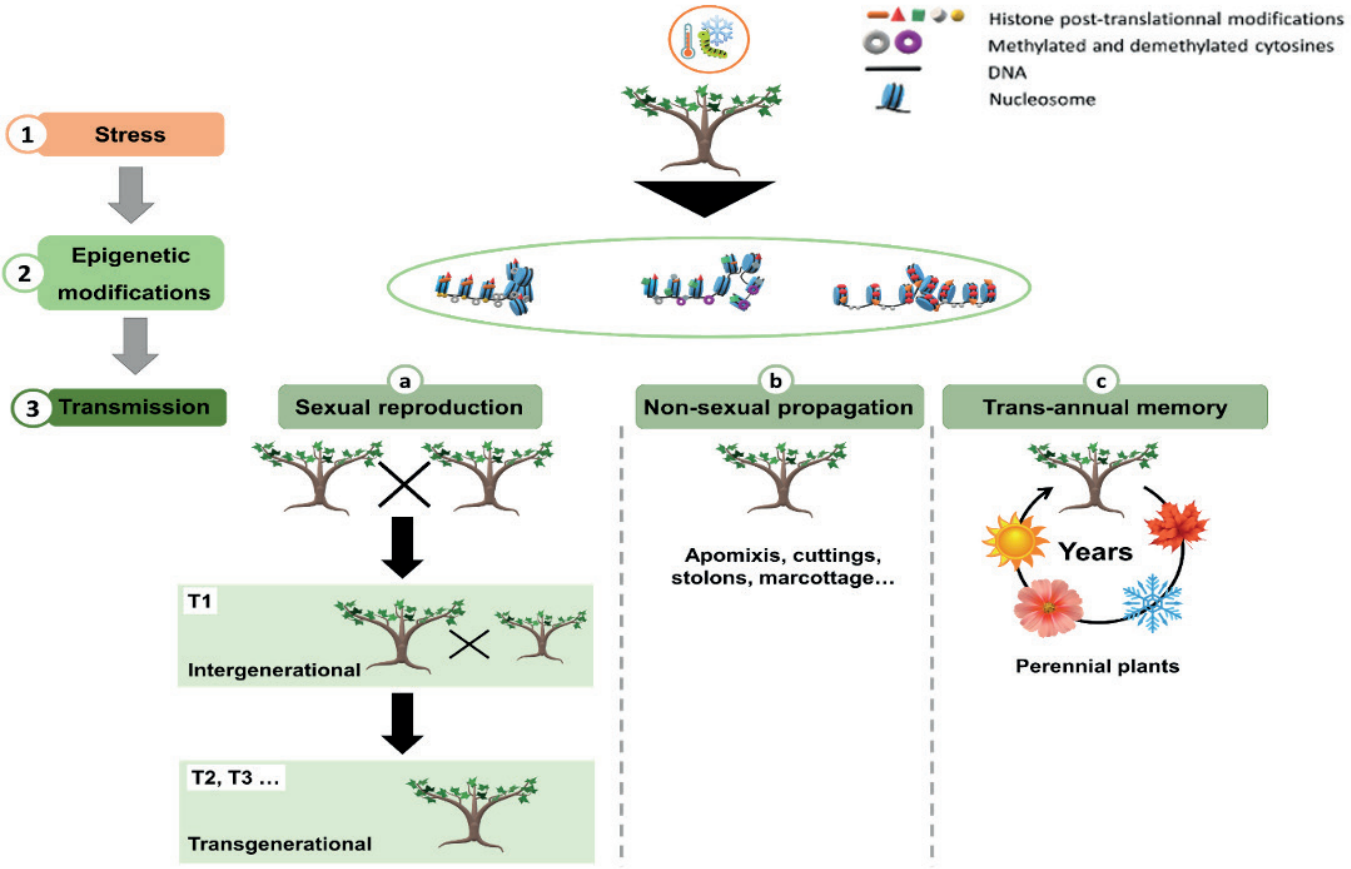


FIGURE 3. Plant epigenetic memories.

Epigenetic information is set up during cell differentiation and will be maintained during cell division. Stresses generated by environmental constraints impact the cell epigenetic landscapes (1) that will be maintained through mitosis (2) defining a somatic epigenetic memory. The transmission of epigenetic marks to further generations (3) can occur through meiosis and reproduction during sexual reproduction (a) through one or eventually several generations (T1, T2, T3). However, the maintenance of an epigenetic memory seems more efficient for non-sexual reproduction (b). Finally, perennial plants may have trans-annual epigenetic memories (c) that allow maintaining part of the epigenetic landscapes defined by their environment.

now shown an epigenetic dialogue during rootstock scion that involves small RNAs mobility between graft partners and changes in DNA methylation (Rubio *et al*., 2022). Graft-dependent DNA methylation signatures were also identified in a study combining grafting with various irrigation treatments (Williams *et al*., 2020).

These results show that epigenetic regulations and memories are likely of major importance in grapevines but require further studies to gain a better understanding of their function in grapevine stress responses and adaptation.

EPIGENETIC MEMORIES OF BIOTIC AND ABIOTIC STRESSES IN PLANTS: APPLICATION TO GRAPEVINE

1. Epigenetic and plant cell memory

Epigenetic regulations are central to the response of plants to both abiotic and biotic stresses. They include DNA methylation remodelling that occurs in response to many different stresses such as exposition to heavy metals, drought, heat or salt stress as well as pathogen attacks, but also involves histone post-translational modifications (HPTMs) and histone variants (for a review, Lämke and Bäurle, 2017). Even more important, plants have developed a memory of stress that relies on various types of mechanisms including the transient accumulation of metabolites, the post-translational modifications of regulatory proteins including transcription factors or MAP kinases and epigenetic mechanisms (Figure 2; Crisp *et al*., 2016).

Importantly, epigenetic mechanisms are likely playing a major role in this context as they embody important aspects of the memory of cells (Pikaard and Mittelsten Scheid, 2014), which is maintained through mitosis during the life of plants and non-sexual reproduction but can also be transmitted to the next generation of plants after sexual reproduction (Anastasiadi *et al*., 2021). Indeed, DNA methylation is maintained by different DNA methyltransferases depending on the C sequence contexts. In the CG and CHG symmetrical context, methylation is maintained respectively by Met1 and CMT3, whereas in the non-symmetrical CHH context, either CMT2 or the RdDM are at work (see the part on epigenetic mechanisms, Zhang *et al*., 2018). Similarly, Histone marks can be maintained during cell division (Jiang and Berger, 2017). These mechanisms allow for maintaining a somatic memory of epigenetic imprints, including those generated by stresses (Figure 2). Indeed, this has been extensively studied in the case of vernalization which provides an excellent example of environmentally driven developmental processes controlled by an epigenetic memory (Luo and He, 2020).

2. Plant priming: what do we know about grapevine

Plant stress somatic memory contributes, among other mechanisms (see above) to their acclimation to the environment, a process also called priming (Liu *et al*., 2022; Mozgova *et al*., 2019). Briefly, priming consists of the response of plants to a first stress (biotic or abiotic) that will be in part memorised. This molecular memory is maintained for some time (from a few days to several weeks) during a recovery period and mobilised when the plant faces subsequent stresses (Figure 3). In that sense, the plant is prepared to better respond to additional stresses (Liu *et al*., 2022; Mozgova *et al*., 2019)

At the molecular level, the first exposure to stress induces a transcriptional response (induction or repression of genes), with some of the genes being differentially expressed and involved in the establishment of a memory of stresses. These so-called "memory genes" have been classified into types I and II which are characterised, respectively, by the maintenance of a transcriptional state induced by the first stress, or by a modified transcriptional response to subsequent stresses as compared to the one triggered by the first stress (Bäurle, 2018). Indeed, maintenance of the stress memory comes at a cost and may be erased in the absence of additional stresses (Bäurle, 2018). Epigenetic processes have been involved in maintaining the transcriptional state of memory genes during plant priming (Figure 3). This somatic memory involves both DNA methylation and HPTMs, and also small RNAs and chromatin remodelers (Mozgova *et al*., 2019), even though their effect and duration might differ. For example, HPTMs were suggested to be the main marks involved in the short-term memory of stresses, while DNA methylation appears more stable and could rather participate in long-term memory and could eventually be transmitted to the next generation of plants after meiosis and fertilisation, contributing to the so-called "Trans- and Intergenerational plant priming" (Gallusci *et al*., 2022).

As far as grapevine is concerned, acclimation to stresses is emerging as a new research field with the initial goal of finding alternatives to pesticides (Delaunois *et al*., 2014), and determining whether pre-treatments with elicitors or bacteria may generate better answers to pathogen attacks. For example, the use of *Pseudomonas fluorescens CHA0* and *Pseudomonas aeruginosa 7NSK2* allowed for eliciting an oxidative burst and phytoalexin synthesis in grape cells and was sufficient to prime grape leaves after subsequent infection with *Botrytis cinerea* (Verhagen *et al*., 2010). Similarly, the treatment of grape berries with methyl jasmonate triggered priming and a better defence response against *B. cinerea* (Wang *et al*., 2015). The ability to prime defence responses was also demonstrated after beta-aminobutyric-acid (BABA) treatments, which induced stilbene synthesis and pathogen-related (PR) protein gene expression. This effect seemed mediated by the activity of the WRKY transcription factor VvWRKY18 (Wang *et al*., 2021). A more comprehensive analysis of priming was performed to investigate the effect of acibenzolar-S-methyl, potassium phosphonate and laminarin treatments on the tolerance to mildew. In this study, transcriptional reprogramming associated with priming was observed in a substance and genotype-dependent way (Pagliarani *et al*., 2020b). However, memory genes were not identified. Priming was also investigated for non-biotic stresses. Recent works have shown that submitting grapevines to

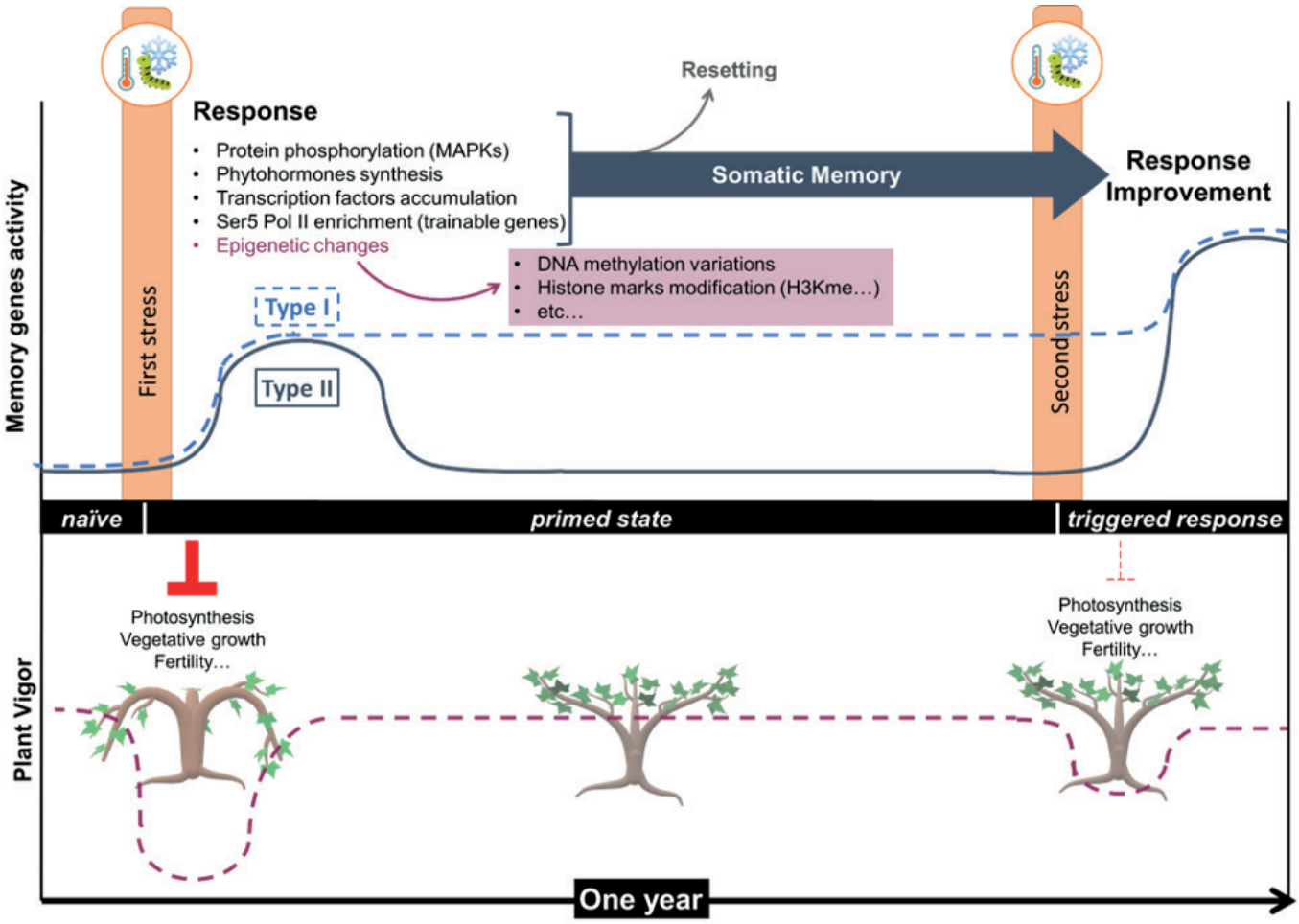


FIGURE 4. Plant priming is mediated by different mechanisms.

When exposed to stress for the first time, naive plants can show important phenotypic responses, like a global decrease in vigour (purple dotted line). This response is associated with proteomic, metabolic, transcriptomic and epigenetic changes. These changes can be either reset to their initial state or (partially) maintained during recovery and constitute a plant somatic memory. As an example, plants possess 'trainable genes' also called 'memory genes' responsive during the first stress that show enhanced activity during a second stress. These genes are subdivided into two categories depending on their activity between the first and second exposition to stress. 'Type I' (dotted blue line) genes triggered activity is maintained, while the one of 'Type II' (dark blue line) genes return to baseline during a period of recovery. Finally, primed plants display improved tolerance to stress, characterised by a lower drop of vigour as compared to the first exposition.

drought stress resulted, the year after, in better growth and contrasted physiological performance, consistent with a trans-annual priming effect, although neither the molecular consequences of the priming treatment nor the mechanisms of trans-annual priming were investigated (Zamorano *et al*., 2021).

So far, very few studies have thoroughly evaluated grapevine plant stress responses and memories using appropriate molecular tools to determine the molecular mechanisms underlying memory effects. Such approaches require combining stress treatments and recovery periods to evaluate priming effects, to a thorough evaluation of the phenotypic, and molecular consequences of the stress, including the analysis of transcriptomic and epigenomic remodelling. This was recently performed to investigate the effect of *Flavesence Doré* in grapevine (Pagliarani *et al*., 2020a), but eventual priming effects were not investigated. Such integrated approaches would however allow identifying memory genes and the underlying epigenetic mechanisms that maintain these genes in an appropriate transcriptional state. Indeed, memory genes and epigenetic processes may vary with the age and genotype of the plant, the organs, the type of stress and/or eliciting molecule.

TRANS AND/OR INTERGENERATIONAL PLANT MEMORIES OF BIOTIC AND ABIOTIC STRESSES

Works in *Arabidopsis thaliana* have shown the stable transmission of epigenetic marks over generations (Figure 4). Whether the memory of stresses can be transmitted to the next generation(s) of plants is however still a matter of intense research (Quadrana and Colot, 2016). Evidence of an intergenerational transmission (one generation) of epigenetic memory of stress has however been demonstrated in model plants and seems preferentially transmitted through the female gamete (Wibowo *et al*., 2016). In contrast, there is no clear

demonstration of a transgenerational (several generations) inheritance of epigenetic information generated by stress. For example, inter- but not trans-generational memory of stress was described in the case of *Arabidopsis thaliana* after exposure to the mild drought stress of a first generation followed by four generations without applying any stress (Van Dooren *et al*., 2020). Mechanisms have already been described that control the balance between resetting and maintenance of epigenetic marks during gametophyte formation, fertilisation and embryo development (Ono and Kinoshita, 2021).

In clonally propagated plants such as grapevine, the progeny is generated by cutting. In this case, the maintenance of epigenetic marks is mediated through mitosis in the stem cells located in meristems. For example, in white clover (González *et al*., 2017) there is a clear demonstration of the maintenance of stress-induced epigenetic imprints in clonally generated progeny when still attached to the mother plant. A similar observation was performed in the progeny of dandelion plants, which is characterised by an apomictic type of reproduction (Verhoeven *et al*., 2010). The functional consequences of such an inheritance on the adaptation capacities of the progeny require additional investigations. Of course, we cannot rule out that when cuttings are generated, as in grapevine, re-juvenilization may occur and reset some or most of the parental epigenetic imprints. However, recent work has shown that even when going through plant regeneration which implies a major developmental reprogramming, the regenerated plant maintains part of the epigenetic imprints of the organ of origin and this impacts its phenotype (Wibowo *et al*., 2018).

As far as grapevine is concerned there is little work performed to investigate how the growing conditions of mother plants will impact the phenotypes of the progeny generated by cuttings, either for scions or rootstocks. Studies in poplar, a woody perennial, have however shown that ramets originating from the same plants but grown in contrasted environments displayed different methylation landscapes consistent with methylation imprints reflecting the environment in which plants are grown, rather than the parental origin (Guarino *et al*., 2015). To what extent these differences in methylation profiles result in a better adaptation to a specific environment has however not been investigated. Similarly in grapevine, the study of methylation variations of grapevine across regions in Australia (Xie *et al*., 2017) showed that methylation patterns varied with geographical location and vineyard management, suggesting that the plant environment, in a broad sense, was shaping the plant methylome. Consistently methylation profiles of Merlot and Pinot Noir (PN) were more affected by their location than by their clonal origin (Baránková *et al*., 2021). These results would suggest that the environment of the plant is more important than its origin in defining the methylome of plants and eventually plant phenotypes.

In contrast, cuttings collected from 60 adult Lombardy poplars growing in different environments, were gathered in a single place and compared for phenology and epigenetic parameters. Results indicate that epigenetic marks could be transferred from parents to asexually multiplied offspring likely reflecting the adaptation to the environment of the parents (Vanden Broeck *et al*., 2018). Similarly, the analysis of DNA methylation patterns of grapevine grown in various Argentinian vineyards indicates that they are more dependent on clonal origin than location (Varela *et al*., 2021). Hence, in these studies the clonal origin of plants seems to significantly impact their methylation landscape, suggesting that the progeny may have inherited the parental adaptation to the environment. However, different approaches between these different studies were used which makes it difficult to compare them and conclude about the relative contribution of parental origin versus the place of growth of the progeny on epigenetic information and phenotypes. In addition, various parameters may affect the memory of parental imprints through non-sexual reproduction such as growth conditions of the progeny, propagation methods, or simply the age of the progeny at the date of analysis because of an eventual epigenetic drift of the progeny, among others.

In this context, more studies are necessary to better understand to what extent and for how long parental epigenetic imprints can be transmitted to asexually reproduced grapevine plants. Important questions to investigate may include: 1) Are growing conditions generating an epigenetic drift that may lead to a better adaptation of plants to their environment? This question could be addressed by analysing the evolution of the epigenetic landscape of individual plants deriving from the same parental plant and grown in the contrasted environment; 2) to what extent environmentally induced changes in the epigenetic landscape are heritable after clonal propagation and 3) confer better adaptation of the progeny to the environment. Indeed, transgenerational priming of plants generated by clonal propagation (considering both rootstocks and scions and their epigenetic interactions) would provide innovative strategies for grapevine adaptation to climate changes, using already cultivated cultivars.

EPI-BREEDING IN GRAPEVINE: WHAT STRATEGIES?

A grapevine is a grafted and clonally propagated plant. This makes it unlikely that the phenotypic diversity observed in this plant is solely due to genetic variations because in most cases genetic variants may remain hidden as heterozygous recessives. Epigenetic variants which may affect similarly both alleles in the genome could therefore be critical in shaping phenotypic variations in this plant. Consistently, clonal diversity within *V. vinifera* varieties was recently associated with methylation changes illustrating the importance of epigenetic markers for intra-varietal diversity (Varela *et al*., 2021).

Grapevine provides a unique system to investigate the consequences of epigenetic variations in clones, their potential role in shaping the phenotypes of plants and opportunities to develop epi-breeding strategies. The generation of Epigenetic Recombinant Inbred Lines (EpiRILs), which takes advantage

of the segregation and recombination between heritable differentially methylated regions (DMRs) to perform (epi) QTL mapping (Quadrana and Colot, 2016), has proven to be an efficient strategy to investigate the contribution of heritable epigenetic variation to agronomic traits. This strategy is based on sexual reproduction where parental lines having the same genotype but with different epigenomes are crossed. After inbreeding over seven generations to fix the epigenetic variations, lines with stable epigenetic differences can be compared in a common genetic background. As examples, Arabidopsis EpiRILs have been generated by crossing a wild-type plant with plants with the same genetic background, but mutated in the gene encoding the DNA METHYLTRANSFERASE-1 (MET1) or DECREASE IN DNA METHYLATION (DDM-1), proteins that are both involved in the maintenance of DNA methylation (reviewed in Catoni and Cortijo, 2018).

EPIRIL populations cannot be developed in crops such as Grapevine that require long generation times and are essentially clonally propagated. In this case, other strategies need to be implemented to investigate the contribution of epigenetic variation to phenotypic diversity and traits of agronomic importance in the absence of DNA sequence polymorphisms. As a first strategy, we have now developed a unique population of isogenic plants displaying epigenomic diversity. This Grapevine "*EpiClonal*" population was initially created from cuttings of a single Pinot Noir plant that were *in vitro* cultured to generate a population of plants with identical genomes and is currently being extended to other cultivars. Stems were subjected to demethylating agents, which cause variable degrees of genome-wide hypomethylation and lead to diverse DNA methylation, eventually to diverse phenotypes. The "*EpiClonal*" populations are currently under vegetative propagation and will be used for methylome and phenotypic analyses. Alternatively, stress conditions may be used to generate an epigenetic drift. Using plants produced from a limited number of mother plants, it is expected to impact the epigenome of plants in different ways if they are grown in contrasted conditions with recurrent stresses, thereby generating epigenetic and phenotypic diversity.

This epigenetic diversity could then be used in different ways: (1) evaluate the resilience of treated versus non-treated plants when subjected to similar stresses; (2) measure the epigenetic drift and identify epi-allelic regions that are critical for the better adaptation of plants to stresses; (3) investigate the stability of epigenetic imprints that have been created over seasons and (4) during plant propagation. Finally, parental priming of rootstocks and scions could provide new ways to develop grapevine propagation strategies better adapted to climate changes building on the epigenetic exchanges existing between the graft partners (Rubio *et al*., 2022). Such populations could also be used for epigenome-wide association studies (EWAS), an approach that has emerged as a powerful way to identify DNA methylation variants associated with phenotypic changes as shown following the identification of an epiallele underlying the metastable mantled somaclonal variant of oil palm (Ong-Abdullah *et al*., 2015).

GENERAL CONCLUSION

There is evidence of various types of epigenetic memories in plants (Gallusci *et al.*, 2022) and this may provide innovative ways to generate lines with new adaptive potential, yet without affecting their genetic information. Figure 4 summarises the different strategies that can be developed in the case of grapevine to use epigenetic regulations and memories as a new lever to develop cultivars and/or rootstocks better adapted to their environment.

Among these tools, the use of agents to modify the epigenome and generate epialleles associated with EWAS will undoubtedly provide information concerning the contribution of epiallelic variation to the phenotypic diversity of grapevine. Similarly, stressing parental plants to generate populations of young plants that are better adapted represents a promising avenue that requires to be thoroughly evaluated to determine the stability over time of parental epigenetic imprints as well as their consequences on the plant's resilience to stresses. This can be implemented both for rootstock and scion, and the epigenetic interactions between partners (Rubio *et al.*, 2022) could provide an additional source of epiallelic variations potentially of use in the context of plant adaptation to climate changes. Indeed, these approaches are non-targeted and require an accurate evaluation of both the epigenetic consequences on plant responses to their environment, on plant production and wine quality as well as the stability of these epigenetic changes.

In addition to these non-targeted induced epiallelic changes, the use of the CrisperCas9 technology to address selectively epigenetic changes at chosen loci (Shin *et al*., 2022) could provide complementary tools that would however require efficient transformation methods and the ability to eliminate the Crisper construction once the epigenetic modification has been performed. In this case, epigenetic consequences of the transformation and regeneration processes should however be thoroughly evaluated, as they may generate unwanted somaclonal variations with long-term effects as already observed in palm oil (Ong-Abdullah *et al.*, 2015). The direct delivery of small RNAs to incipient cells using nanoparticles could be another way that needs to be investigated, to generate new DNA methylation imprints by the RdDM pathway at selected genes to repress their expression.

At present, analysing the range of epigenomic variations in grapevine depending on clones and area of growth, as well as on genotypes, is an absolute requirement to determine environmentally driven epigenetic drifts, their interactions with plant genotypes and genomic structure and their consequences on plant phenotypes.

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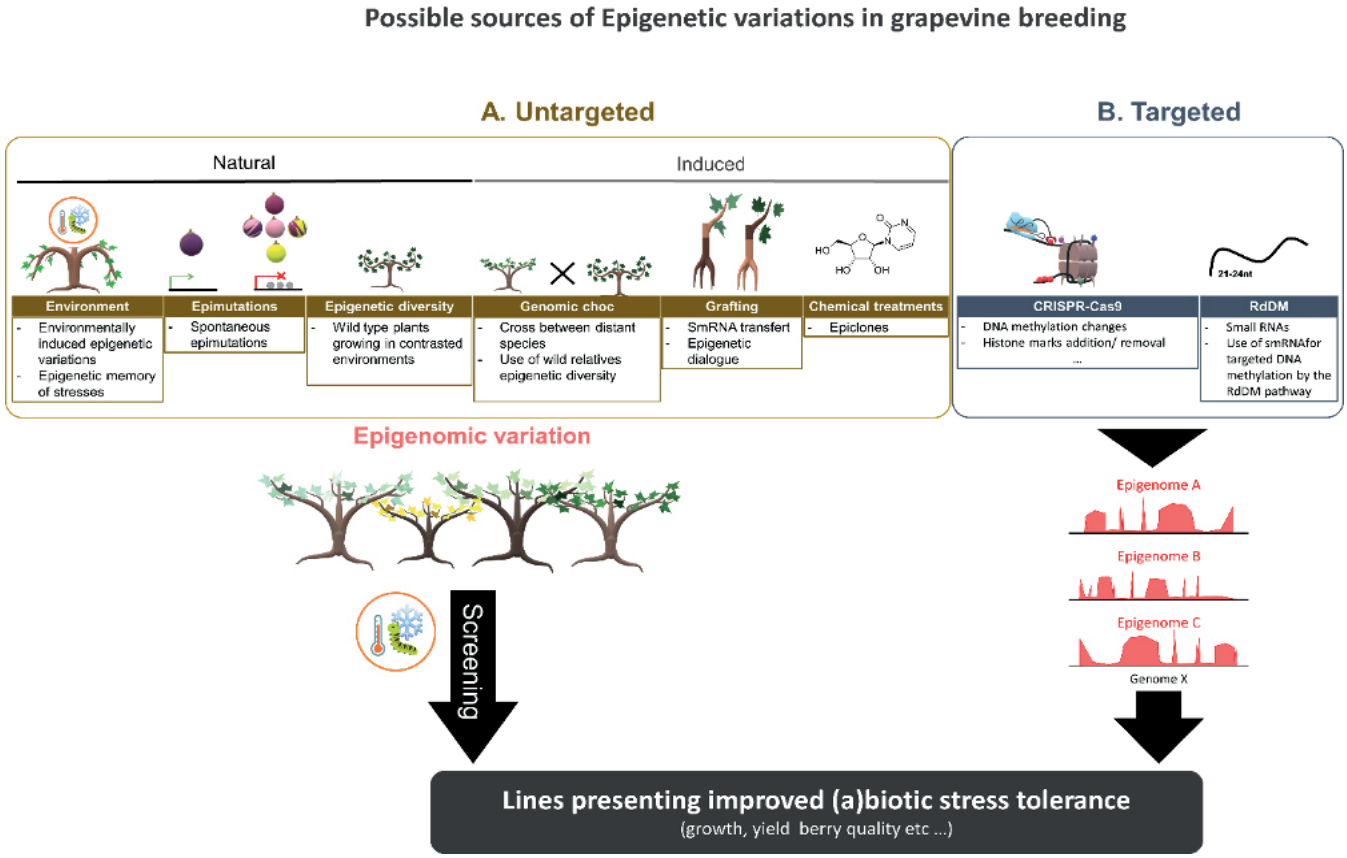


FIGURE 5. Possible sources of epigenetic diversity for grapevine improvement.

(A) Untargeted epigenetic variation can occur naturally or be generated experimentally. Epigenetic diversity can be found in natural populations or occur spontaneously in cultivated populations. Environmental stresses may also result in epigenetic variations that are memorized by plants and generate epigenomic variations. Epigenetic variations can be created when two distantly related species are crossed (genomic choc). An epigenetic dialogue occurs during grafting that impacts the epigenome of both partners, which may lead to new epiallelic combinations. In vitro propagation of plants in the presence of methylation inhibitors generates randomly hypomethylated genomes that result in clones with modified epigenomes and identical genomes.

(B) Targeted epigenetic changes can be created using epigenome editing for example using CRISPR-ca9. The use of specific small RNAs (24nt) can allow addressing the novo methylation by the RdDM at specific loci

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