

Epigenetic Regulation in Fleshy Fruit: Perspective for Grape Berry Development and Ripening

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Abstract

Epigenetic regulation mainly refers to histone post-translational modifications and DNA methylation, which are critical to plant gene regulation and contribute to the development of plants and to their response to the environment. Recent molecular and epigenomic studies have shown that epigenetic regulations play critical roles in tomato fruit development and ripening, the current model for climacteric fruit. This led to a new model of ripening control where active DNA demethylation

plays a central role being necessary to the induction of several genes that control fruit ripening. Whether this is a general model applying to all type of fruit, including non-climacteric fruit for which grape berry stands as a general model, is an open question that requires investigating the genome-wide variations of epigenetic marks during fruit development and ripening in many different species. Finally, the potential roles of epigenetic regulations in grapevine, a perennial, grafted, and clonally propagated plant, are discussed.

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9.1 Introduction: Relevance of Epigenetic Regulations in Plants

In eukaryotes, DNA is tightly associated with histones to form the chromatin, a highly dynamic structure that plays critical roles in genome functioning. Chromatin is made of elementary units called nucleosomes that are composed of octamers of the core histones (H2A, H2B, H3, and H4) around which 147 bp of DNA is rolled up. Nucleosomes are separated by a 50-bp-long linker DNA that interacts with histone H1. Traditionally, two distinct chromatin states have been described: the highly condensed heterochromatin, which is considered as inactive, and euchromatin which corresponds to a less condensed and

transcriptionally active chromatin state. Indeed, dynamic changes on chromatin play critical roles in gene regulation and have therefore been the subject of intensive studies over the last decades both in animals and in plants (Exner and Hennig 2008; Zheng and Liu 2019).

Epigenetics was initially defined as “the branch of biology which studies the causal interactions between genes and their products which bring the phenotype into being” (Waddington 1942). Epigenetics now refers to “the study of changes in gene function that are mitotically and/or meiotically heritable and that do not entail change in DNA sequence” (Wu and Morris 2001). Epigenetic regulations are mediated by the so-called epigenetic marks that include the methylation of the cytosines on the 5th carbon (5-methylCytosine, 5mC) as well as several histone post-translational modifications (HPTMs), but also involve small RNAs and histone variants (Law and Jacobsen 2010; Maeji and Nishimura 2018; Rothbart and Strahl 2014). Both types of marks contribute to defining specific chromatin states and consequent gene expression patterns that can be maintained after cell division during tissue and organ development (Birnbaum and Roudier 2017; Eichten et al. 2014; Pikaard and Scheid 2014).

Epigenetic modifications are now emerging as crucial players controlling various aspects of plant development, such as for example transitions between developmental phases (Trindade et al. 2017), plant reproduction (Wang and Köhler 2017), root (Kawakatsu et al. 2016), seed (Kawakatsu et al. 2017), and fruit development (Gallusci et al. 2016; Giovannoni et al. 2017). It also participates in the response of plants to environmental stresses (Chinnusamy and Zhu 2009; Crisp et al. 2016).

In this chapter, we will mainly focus on the role of epigenetic regulations in fleshy fruit, an organ of primary importance for plants as it insures seed dispersal and for humankind, because fleshy fruits are an important source of nutrients in human nutrition (Klee and Giovannoni 2011) and provide raw material for products of high economical value such as wine. Studies in tomato, grape, strawberry, and others have

now shown that the development and ripening of fleshy fruit rely on the establishment and maintenance of differential gene expression patterns (Alba 2005; Osorio et al. 2011) and complex regulatory pathways that involve both genetic and hormonal controls critical at these developmental phases (Osorio et al. 2013). However, several studies have now shown that both DNA methylation and histone PTMs also regulate fruit development and ripening (Bucher et al. 2018; Gallusci et al. 2016; Giovannoni et al. 2017) indicating that epigenetic regulations require to be considered as well. Most of these studies have been performed on tomato, the model plant for climacteric fruit. However, tomato fruit presents specific developmental and physiological features including high endoreduplication levels and a monophasic growth curve. Therefore, it remains unclear whether similar mechanisms are operating in other fruits with different characteristics, such as grape, the model for non-climacteric fruit.

Here, we summarize the current knowledge of epigenetic mechanisms in plants and present the most recent studies highlighting the role of epigenetic regulations in fruit development and ripening. As a conclusion, we discuss the specificity of grape as a grafted perennial plant that is clonally propagated and develops non-climacteric fruit.

9.2 Fleshy Fruit Development and Ripening: Specificities of Grape Berries

Fruit is an organ specific to angiosperms designed for seed protection and dispersal that has long been considered essential in the human diet because it contains fibers, vitamins, carbohydrates, and antioxidants that are essential to humans (Klee and Giovannoni 2011; Seymour et al. 2013). Most fruits develop from ovaries, although accessory tissues, for example the receptacle in strawberry, may be used as well (Seymour et al. 2013). The development of fleshy fruit is in most cases initiated by fertilization and is characterized by two main steps that precede fruit ripening: (1) a cell division phase which is

initiated shortly after pollination and followed by (2) a cell expansion phase that is responsible for the increase in fruit size (Gillaspy et al. 1993). In contrast to dry fruits that undergo lignification, fleshy fruit enters a complex ripening process characterized by extensive metabolic modifications such as soluble sugar accumulation, cell wall degradation, and synthesis of a wide range of secondary compounds of high nutritional value such as carotenoids or anthocyanins, and several vitamins. In most cases, fruit ripening results in significant changes in fruit appearance, including fruit color modifications and fruit softening (Lee et al. 2012; Seymour et al. 2013).

Among fleshy fruit, grape berry presents specific developmental features. In contrast to most fruits that present a typical simple sigmoid growth curve, grape berry growth follows a double sigmoid curve as fruit size increases both before and after the induction of ripening (Conde et al. 2007; Serrano et al. 2017). The first increase in berry size starts shortly after fruit set and is due to cell division and subsequent cell expansion. It is characterized by organic acid accumulation in vacuoles and the synthesis of tannins and hydroxycinnamates. The berry size stops to increase during the so-called lag phase that precedes the “véraison stage,” which is characterized by berry softening, ABA synthesis, and initiation of sugar and anthocyanin accumulation (Castellarin et al. 2015). Following, grape berry size increases again due to additional cell expansion events in the mesocarp. This second growth phase, which occurs during ripening, is characterized by important metabolic changes that include the accumulation of glucose and fructose along with a decrease in organic acid levels, berry softening, and the synthesis of precursors of various aromatic compounds including terpenes, isoprenoids, esters, and thiols.

Fleshy fruits have been classified based on the physiological mechanisms that control the induction of ripening. Climacteric fruits for which tomato stands as a model (Giovannoni et al. 2017) are characterized by an intense respiratory burst associated with ethylene synthesis that precedes fruit ripening induction. This contrasts with non-climacteric fruits such as grape and

strawberry, for which no specific physiological parameter that marks the initiation of ripening has been identified (Bapat et al. 2010), even if hormones, including ethylene and ABA, are now known to have important roles in the ripening of this type of fruit (Fortes et al. 2015). Genetic control of ripening has also been demonstrated for climacteric fruit, mainly in the tomato model, and several mutations affecting essential regulators of ripening have been described in this plant (Gapper et al. 2014; Bucher et al. 2018; Gallusci et al. 2016). The recent discovery that epigenetic regulators are major players in the control of fruit development, ripening, and senescence has deeply changed the proposed models describing the regulation of fruit development and raises the question of the general function of such mechanisms in all types of fruit. So far, most studies indicate that epigenetic regulations may be important in other types of fruit.

9.3 Epigenetic Mechanisms

Epigenetic regulations are based on two main mechanisms, histone post-translational modifications (HPTMs) and DNA methylation, and also include additional processes such as short interfering RNAs (siRNAs) synthesis and specific histone isoforms, called histone variants. These mechanisms have been the subject of many recent reviews (see, e.g., Maeji and Nishimura 2018) and will be only summarized here with a focus on the most recent findings.

9.3.1 Histone Post-translational Modifications

The mechanisms responsible for histone post-translational modifications (HPTMs) are conserved in plants and animals (Feng and Jacobsen 2011; Fuchs et al. 2006). The following part presents these conserved mechanisms using examples taken from plant models (except when data were obtained from animal models only) and discusses a few differences discriminating plants from animals.

9.3.1.1 Numerous Histone Post-translational Modifications and Histone Variants Contribute to the Epigenetic Information

All histones are subjected to a wide variety of post-translational modifications that include methylation, acetylation, phosphorylation, ubiquitylation, sumoylation, and ADP ribosylation (Bannister and Kouzarides 2011; Berger 2007; Feng and Jacobsen 2011; Jenuwein and Allis 2001). These modifications affect various amino acids at different positions. The nucleosomal histones are mostly modified at their NH₂ terminus which protrudes out of the nucleosome. In addition, histone H2A, histone H3, and histone H1 are encoded by small gene families, allowing the production of different isoforms usually referred to as histone variants that bear specific roles and may be subjected to differential post-translational modifications (Jiang and Berger 2017; Talbert and Henikoff 2017). Importantly, most histone marks are found both in plants and in animals, but the same histone mark can have a different distribution and physiological function in different organisms. A striking example is the mark H3K9me₃ which is mostly associated with heterochromatin in organisms ranging from fission yeast to humans (Becker et al. 2016), but it is typically found in euchromatin in *Arabidopsis* (Roudier et al. 2011).

Histone modifications and histone variants control several processes linked to genome function, such as DNA replication, DNA repair, DNA recombination, and transcriptional activation/inactivation (Vergara and Gutierrez 2017). Most studies have focused on their function in gene expression, which relies on two main mechanisms (Bannister and Kouzarides 2011; Berger 2007; Engelhorn et al. 2014). First HPTMs, like histone acetylation, neutralize the positive charge of histones and weaken the interaction between histones and the negatively charged DNA molecule leading to an increased DNA accessibility to the transcriptional machinery. Recent data based on a multiscale

computational study have shown that histone lysine acetylation also unfolds chromatin by decreasing tail availability for inter-nucleosome interactions, which are important for the chromatin fiber compaction (Collepardo-Guevara et al. 2015). In addition, HPTMs are recognized by a diverse set of effector proteins, also called histone readers, which participate in the control of gene expression, for example chromatin remodeling proteins or transcriptional regulators. Hence, a large array of protein domains has been characterized, which recognize and bind to specific histone modifications. Some of the HPTM readers are directly responsible for a specific functional outcome such as the DNA methyltransferase CMT3 which recognizes H3K9me₂ (Du et al. 2012; Lindroth et al. 2004) and is responsible for CHG methylation (Lindroth et al. 2001). Alternatively, HPTM readers can act through their interaction with effector proteins. For example, the *Arabidopsis* MORF-related gene (MRG) group proteins, MRG1 and MRG2, recognize the H3K4me₃/H3K36me₃ marks on the *FLOWERING LOCUS T* (*FT*) promoter; this interaction favors the activation of *FT* transcription through a physical interaction between MRG1/MRG2 and the transcription factor CONSTANS (Bu et al. 2014). Because they rely on a number of different protein partners, such mechanisms can be precisely controlled. Finally, recent data suggest that HPTMs play a role in the 3D organization of genomic DNA, contributing to the formation of specific nuclear territories, characterized by precise expression output (Liu et al. 2016; Rodriguez-Granados et al. 2016; Veluchamy et al. 2016).

9.3.1.2 The Genome-Wide Distribution of HPTMs Shapes the Epigenetic Landscape

The recent development of genome-wide analysis of epigenetic mark distribution has shown that histone PTMs together with DNA methylation (see below) can form specific combinations that define genome territories with either active or repressive chromatin states in multiple organisms from metazoa (Baker 2011) to plants, including

rice (Li et al. 2008), *Arabidopsis* (Luo et al. 2013; Roudier et al. 2011; Sequeira-Mendes et al. 2014; Wang et al. 2015), and barley (Baker et al. 2015). These studies allowed the identification of a finite number of chromatin states along chromosomes, characterized by distinct sets of epigenetic marks. Interestingly, genomic elements are often distinguished by specific chromatin states. For example, in *Arabidopsis*, silent heterochromatin is associated with H3.1, H3K9me2, H3K27me1, and 5mC, and the transcriptional start site (TSS) of many actively transcribed genes with a combination of H2Bub, H3K36me3, and H3K4me3. Alternatively, repressed genes present in euchromatic regions are associated with H3K27me3 within a nucleosome context enriched in H3.1 (Roudier et al. 2011; Sequeira-Mendes et al. 2014).

Interestingly, some genes are associated with both active and repressive marks, as illustrated by the chromatin state 2 defined by Sequeira-Mendes et al. (2014), where H3K4me2 and H3K27me2 coexist. Such bivalent chromatin states have been described at genes coding for important developmental regulators such as *AGAMOUS* (Saleh et al. 2007) or floral integrators (Qian et al. 2018) and could be necessary for fine-tuning gene expression.

9.3.1.3 HPTMs Dynamic Is Controlled by Specific Enzymes

Active and repressive histone marks are established and removed by specific enzymes referred to as HPTM writers and erasers, respectively. The level of each HPTM is therefore determined in a dynamic fashion, by the relative abundance/activity of its specific writer(s) and eraser(s) (Fig. 9.1). Although HPTMs are reversible marks, their stability is variable. For example, histone acetylation is a very dynamic epigenetic mark. The estimation of H3 and H4 acetylation turnover rates in human cells revealed very short half-lives (Zheng et al. 2013), with 12 histone sites displaying half-life below one hour (Weinert et al. 2018). As a consequence, modification of histone acetylation status could be essential when rapid changes in gene expression are required, for example in response to

environmental stimuli (Barth and Imhof 2010). On the contrary, H3K27me3 was initially considered a very stable epigenetic mark that was conserved through cell division perpetuating the stable repressive state of the chromatin at specific loci. Consequently, H3K27me3 is considered a major determinant of cell identity, although it is now clearly established that this mark can be actively removed by the Jumonji-type of histone demethylases (Chen et al. 2011; Liu et al. 2010; Xiao et al. 2016).

Many genes coding for HPTM writers and erasers have been identified and functionally characterized in *Arabidopsis* (Fig. 9.1). Most studies have focused on histone methylation and acetylation, so that other HPTMs, such as histone phosphorylation or sumoylation, have been overlooked. Over the past decade, functional analyses of writers and erasers have also been conducted in a few other models and crop species, like tomato (Boureau et al. 2016; How Kit et al. 2010), rice (Jiang et al. 2018a, b; Li et al. 2014; Liu et al. 2017; Zheng et al. 2015), *Brassica napus* (Jiang et al. 2018c), poplar (Fan et al. 2018), wheat (Liu et al. 2018), and maize (Forestan et al. 2018; Rossi et al. 2007). These studies are mainly based on the characterization of genes presenting homologies with those originally identified in *Arabidopsis*. As shown in Fig. 9.1, each histone mark is set up by a specific set of enzymes, which are frequently specialized in the addition of a precise number of modifications. For example, whereas *ARABIDOPSIS TRITHORAX-RELATED PROTEIN 5* (*ATRX5*) and *ATRX6* of the trithorax group are responsible for the addition of one methyl group at histone 3 lysine 27 (H3K27me1) (Jacob et al. 2009). Enhancer of Zeste proteins from the Polycomb group family are part of the Polycomb Repressive Complex 2 (PRC2) and are in charge of the addition of 2 and 3 methyl groups at the same residue (H3K27me3) (Liu et al. 2010; Fig. 9.1).

In addition, most writers and erasers function as multiprotein complexes. As mentioned above, the Enhancer of Zeste (*E(z)*) proteins which catalyze the H3K27 trimethylation is part of the PRC2 complex. PRC2s contain three additional core proteins, a protein of the Suppressor of

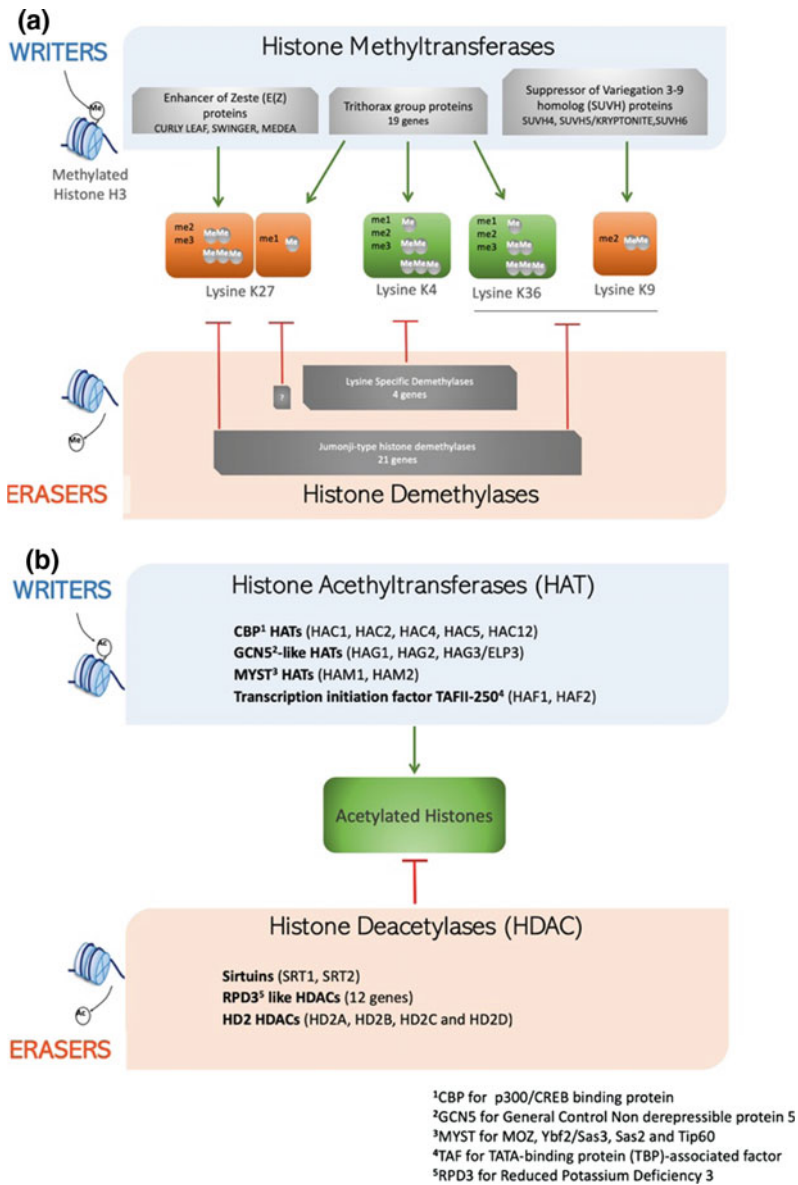


Fig. 9.1 Histone H3 major post-translational modifications and corresponding enzymes. **a** Proteins responsible for histone H3 methylation/demethylation. Depending on the modified lysine residue (lysine K4, K9, K27, or K36), different protein families are involved. Moreover, different proteins may be required depending on the number of methyl residues added/eliminated, as reviewed in Liu et al. (2010); Chen et al. (2011); and (Xiao et al. 2016). **b** Proteins responsible for histone acetylation and

deacetylation. For each type of regulators, the number of genes found in the Arabidopsis genome is specified. In a few cases, the name of these genes is indicated. Of note, for gene families which include a large number of genes, such as the trithorax group proteins, only a few genes have been functionally characterized. The transcriptional state (active or inactive) mainly associated with each HPTM is indicated using the following color code: active in green/inactive in red

Zeste 12 (Su (z)12) family, a protein of the Extra Sex Comb (ESC) family, and a Multicopy Suppressor of IRA 1 (MSI) protein. The four PRC2

core proteins are necessary for PRC2 to function in vivo (Schubert et al. 2005), but only the E(z) protein harbors the methyltransferase catalytic

domain (the so-called SET domain). Many histone deacetylases (HDACs) have also been shown to associate with other proteins to form multi-subunit complexes, suggesting that they function cooperatively with other epigenetic regulators and in association with transcription factors (for recent results, see Hung et al. 2018; Kim et al. 2016; and Yu et al. 2017).

Another important common trait of writers and erasers in plants is that they are both encoded by multigene families leading to the production of multiple isoforms that controls each histone PTM. In *Arabidopsis*, for example, the E(z) proteins are encoded by three genes, respectively, *CURLY LEAF (CLF)*, *SWINGER (SWN)*, and *MEDEA (MEA)*. Hence, a variety of PRC2 complexes are produced, which act in a redundant manner and/or at distinct developmental transitions during the life cycle (Chanvivattana et al. 2004; Derkacheva and Hennig 2013; Kinoshita et al. 2001; Mozgova and Hennig 2015).

9.3.1.4 A Diversity of Mechanisms Is Involved in the Targeting of Histone Writers/Erasers

The molecular mechanisms responsible for the recruitment of the epigenetic writers and erasers to their specific target loci have been a long-standing question. Recent data suggest that different mechanisms may be involved (Deng et al. 2018). Although this does not appear as a general feature, some enzymes responsible for histone mark editing contain DNA-binding domains, which participate in their recruitment at specific DNA consensus sequences. As an example, relative of early flowering, also known as Jumonji domain-containing protein 12 (JMJ12), which specifically demethylates H3K27me3 (Lu et al. 2011), recognizes a CTCTGYTY motif through its four Cys2His2 zinc fingers (Cui et al. 2016; Li et al. 2016). A second and more general mechanism involves transcription factors and corepressors, which can recruit epigenetic regulators either through direct protein–protein interactions or because they are partners in the same multi-subunit complexes (Vachon et al. 2018). This has been demonstrated

for a number of different epigenetic regulators including PcG proteins (Questa et al. 2016; Roy et al. 2018; Xiao et al. 2017; Yuan et al. 2016; Zhou et al. 2018), Jumonji domain-containing histone demethylases (Cheng et al. 2018b; Hou et al. 2014; Ning et al. 2015; Zhang et al. 2015), and HDACs (Cheng et al. 2018c; Tang et al. 2016a, 2017). In addition, transcription factor binding at specific gene regulatory regions can induce the displacement of writers/erasers from their target loci, as demonstrates at least in two plant studies (Luo et al. 2018; Sun et al. 2014). Non-coding RNAs are also involved in the targeting of HPTM regulators. Two long non-coding RNAs play a role in the repression of FLOWERING LOCUS C (FLC) expression by PcG proteins (Heo and Sung 2011; Kim et al. 2017; Kim and Sung 2017), participating in their recruitment through an uncharacterized mechanism (Kim et al. 2017). Also, an intronic non-coding RNA was shown to be necessary for the CLF-dependent repression of AGAMOUS (Wu et al. 2018). Whether this mechanism is more general remains to be demonstrated. Finally, a few epigenetic regulators are recruited through their interaction with other epigenetic marks, or of histone variants, thereby generating specific epigenetic mark combinations. For example, according to the canonical model, PRC1 complexes are recruited to PcG target genes through the recognition of H3K27me3, leading to the addition of the H2Ub marks at the same loci and to the stable repression of the corresponding genes (Del Prete et al. 2015).

Altogether, these mechanisms ensure that writers and erasers are recruited only at specific loci at specific times. In addition, HPTM editing can be controlled through the regulation of the production of the writers/erasers and of their enzymatic activity.

9.3.1.5 Regulation of HPTM Remodeling

A few epigenetic regulators are expressed at specific developmental stages or in response to precise environmental changes. For example, MEDEA, an E(z) coding for an H3K27me3 methyltransferase, is specifically expressed in the

female gametophyte, in the endosperm or in response to an infection by a pathogen (Chaudhury et al. 1997; Roy et al. 2018; Spillane et al. 2000; Yadegari et al. 2000). Another example is the histone demethylase JMJ30, whose expression oscillates with a circadian rhythm and plays a role in the regulation of the period length (Jones et al. 2010; Lu et al. 2011). Hence, as a first regulation level, cells can control the timing of epigenetic changes by a tight regulation of the synthesis of the epigenetic writers/erasers, at least in some specific cases. In addition, epigenetic regulators can be post-translationally regulated through direct protein–protein interactions. For example, the activity of the histone deacetylase HDA6 has been shown to be regulated by phosphorylation (Yu et al. 2017), the activity of histone methyltransferase ATX1 by O-GlcNacylation (Xing et al. 2018), and the activity of the histone methyltransferase CLF by an F-box protein responsible for protein ubiquitylation before their degradation through the ubiquitin–26S proteasome (Woong et al. 2011). Moreover, as described above (Sect. 9.3.1.4), histone modifiers can also be controlled by transcription factors through a regulation of their recruitment and/or eviction to/from their target sites. On top of that, an increasing number of data suggest that HPTM is under metabolic control (for a review, see: Shen et al. 2016). Indeed, several regulators use metabolites as substrate or cofactor: for example, histone acetyltransferases, which necessitate acetyl-coA, and histone methyltransferases, which depend on S-adenosyl methionine availability.

As described in the above paragraph, our knowledge about the mechanisms underlying gene expression regulation through HPTM is rapidly growing, revealing a tight cross talk between histone modifiers, chromatin remodeling complexes, and the transcription machinery (Ojolo et al. 2018). In addition, multiple histone-related epigenetic regulators may be required in a highly coordinated manner for the proper control of gene expression, as it has been demonstrated for *FLOWERING LOCUS C (FLC)* coding for a central floral repressor in Arabidopsis (Berry and Dean 2015; Fletcher 2017;

Hepworth and Dean 2015; Whittaker and Dean 2017). In addition, HPTMs do not act alone, but in combination with DNA methylation. Several data suggest a functional coupling between histone and DNA methylation, including the aforementioned interaction between H3K9me2 and the DNA methyltransferase CMT3 (for reviews: Du et al. 2015; Torres and Fujimori 2015).

9.3.2 DNA Methylation

DNA methylation is an important and a highly conserved epigenetic mark that has been studied in detail in fungi, animals, and plants and plays fundamental roles in genome functioning and protection. It refers to the transfer of a methyl group to the fifth position of the cytosine ring of nuclear genomic DNA to form 5 methylcytosine. In contrast to mammalian where DNA methylation mainly occurs at CG sites, in plants genomic DNA can be methylated in all cytosine sequence contexts, including the symmetrical CG, CHG motives, and the non-symmetrical CHH motif (which H represents A, T, or C) (He et al. 2011; Law and Jacobsen 2010). Each sequence context requires different mechanisms for establishment and maintenance of DNA methylation (Fig. 9.2).

9.3.2.1 Mechanisms of DNA Methylation in Plants

The mechanisms that control both initiation and maintenance of DNA methylation have received much attention in Arabidopsis (Matzke et al. 2015; Matzke and Mosher 2014; Law and Jacobsen 2010), although studies have also been performed in crop plants including corn, rice, and tomato (Chodavarapu et al. 2012; Corem et al. 2018; Eichten et al. 2013; Fu et al. 2018a; Hu et al. 2014; Li et al. 2012). DNA replication is a semiconservative process that leads to the formation of hemi-methylated DNA molecules. During replication, only non-methylated cytosines are incorporated in the newly synthesized DNA strand. Cells have therefore developed specific mechanisms to fully re-establish DNA methylation patterns. In mammalian, this is insured by the enzyme, Dnmt1, that recognizes

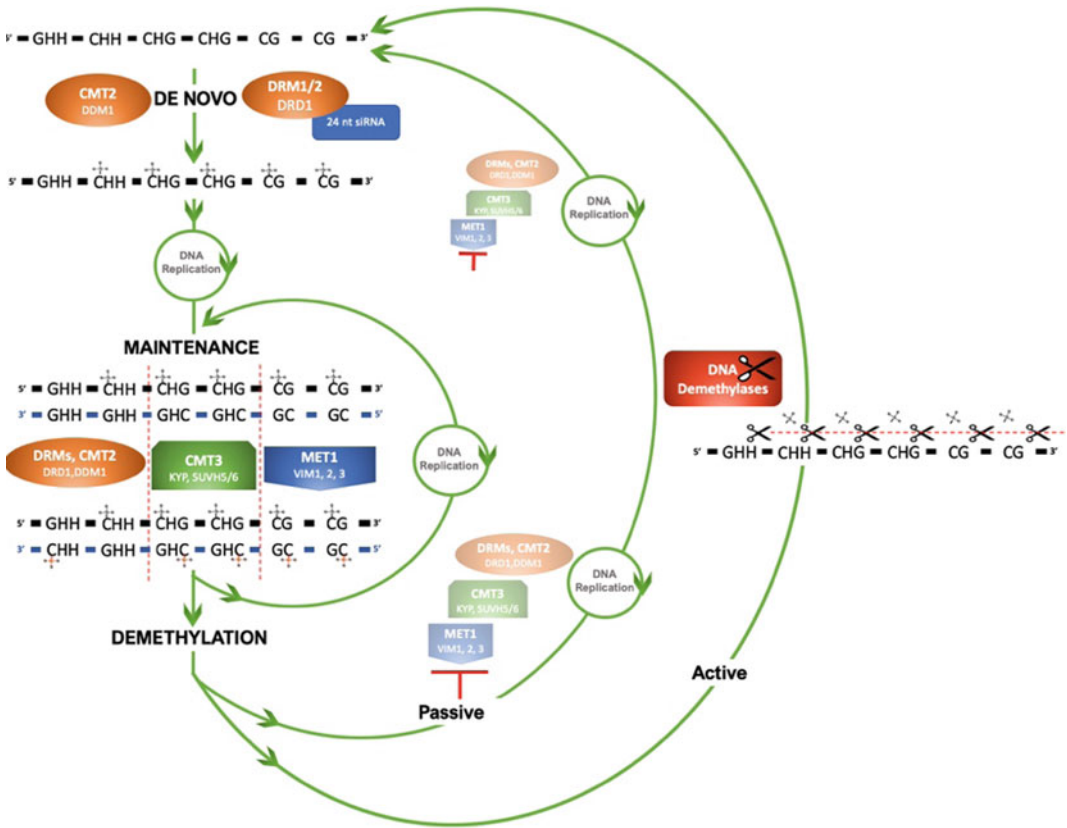


Fig. 9.2 Mechanisms of de novo and maintenance of DNA methylation in plants. DNA methyltransferases and demethylases are involved in 5mC de novo methylation, maintenance of methylation, and demethylation in higher plants. Names of enzymes are those identified in the Arabidopsis model. De novo DNA methylation is set up by the RNA-directed DNA methylation (RdDM) pathway involving the DRM1/2 methyltransferases, DRD1, and 24nt-long small RNAs, and by the chromomethylase CMT2 with DDM1 in the CHH sequence context at heterochromatic regions (Zemach et al. 2013). After replication, newly produced DNA is hemi-methylated at CG and CHG symmetrical sites, but at the non-symmetrical CHH sites only one of the two newly synthesized DNA molecules is not methylated. Maintenance of methylation in the CG context depends on MET1 and VIM1, 2, and 3, and maintenance in the CHG context is catalyzed by CMT3. CHH maintenance of

methylation depends both on the RdDM pathway and on CMT2 activity. Both CMTs are dependent on histone methylation mediated by KYP and SUVH5 and 6. DNA demethylation can occur passively in a replication-dependent way, when the methylation machinery is not or poorly active. 5mC cytosine can be actively removed by DNA glycosylase/lyase, also called DNA demethylase, independently from DNA replication. Newly synthesized DNA strands are colored in deep blue. Shaded figures represent enzymes showing reduced activity. Enzyme names are from Arabidopsis. DRM1/2, CMT2/3 (chromomethylase2/3), MET1 (cytosine DNA methyltransferase 1), VIM1-3 (variant in methylation1-3), 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)

hemi-methylated DNA template at CG motives (Law and Jacobsen 2010). In plants, different mechanisms that are specific to each of the sequence contexts for DNA methylation have been identified that fulfill these tasks (Fig. 9.2). The DNA methyltransferase 1 (MET1), which is

orthologous to the mammalian Dnmt1 (Achour et al. 2008; Sharif et al. 2007), is recruited to hemi-methylated DNA by VIM1 and 2 (variant in methylation 1 and 2) and insures the maintenance of methylation at CG sites (Vongs et al. 1993). Both VIM1 and 2 proteins contain an

SRA (SET- and RING-associated) domain that mediates their binding to hemi-methylated DNA (Kim et al. 2014; Woo et al. 2008). The CHG methylation is maintained by plant-specific DNA methyltransferases, namely the chromomethylases (CMTs), that include CMT3 in Arabidopsis (Bartee et al. 2001; Bewick et al. 2017; Jackson et al. 2002) and its maize homolog ZMET2 (Du et al. 2012; Papa et al. 2001). CMTs contain a BAH domain (bromo-adjacent homology) and a chromodomain (chromatin organization modifier) that is required to their binding to histone H3 when dimethylated on lysine K9 (H3K9me2). Genome-wide analysis of CMT3 distribution has shown that it co-localizes with H3K9me2, an interaction that seems necessary for CMT3 activity in vivo (Bernatavichute et al. 2008; Du et al. 2012). Based on the current model, CMT3 and ZMET2 are recruited to their targets following binding to H3K9me2, which is set up by suppressor of variegation homolog 4 (SUVH4)/KRYPTONITE (KYP), SUVH5, and SUVH6 (Bartee et al. 2001; Du et al. 2014; Gouil and Baulcombe 2016; Jackson et al. 2002). Consistent with this view, mutations impairing SUVH4/KRYP present a dramatic reduction in both H3K9me2 and CHG methylation levels (Jackson et al. 2002; Malagnac et al. 2002). As SUVH4/KRYP contains an SRA domain that allows its recruitment to methylated DNA, it is thought that CMTs and KRYP are working in a regulatory loop to maintain CHG methylation (Du et al. 2014). Finally, CHG methylation and H3K9me2 interactions are further highlighted by the study of the *ibm1* mutant (increase in bonsai methylation) that shows an increased level of both H3K9me and CHG methylation at active genes (Miura et al. 2009). The *IBM1* gene encodes a Jumonji type of histone demethylase necessary to eliminate H3K9me2 at genes, thereby preventing CHG methylation and insuring an active chromatin state (Inagaki et al. 2010; Saze et al. 2008). Recently in Arabidopsis, CMT2 was shown to maintain CHH and CHG methylation in large heterochromatin peri-centromeric regions enriched in large transposons (TEs) (Zemach et al. 2013), most likely

via its interaction with the H3K9me2 histone PTMs (Stroud et al. 2014).

Maintenance of methylation at CHH sites and initiation of DNA methylation at non-methylated sites irrespective to the sequence context are both catalyzed by a third class of DNA methyltransferases, the domain rearranged methyltransferases (DRMs; reviewed in Law and Jacobsen 2010). These enzymes are directed to their target loci by 24 nt small interfering RNA (siRNA) in a process named RNA-directed DNA methylation (RdDM; Matzke et al. 2015). The synthesis of these small RNAs has been studied in great details in Arabidopsis over the last decades and will not be discussed here as several recent reviews are available (Matzke et al. 2015; Matzke and Mosher 2014; Wendte and Pikaard 2017).

9.3.2.2 DNA Demethylation

Although DNA methylation is considered as a stable epigenetic mark, reprogramming of DNA methylation patterns has been observed in various plant tissues and at specific developmental stages (Li et al. 2018). DNA methylation can be either actively removed or passively lost (Fig. 9.2; Law and Jacobsen 2010). Passive demethylation occurs after DNA replication when non-methylated cytosines incorporated in the newly synthesized DNA strand cannot be methylated because the DNA methylation machinery is not operating. This results in a rapid and non-specific dilution of methylation as observed in *met1* and other mutants affected in methylation control that presented a general decrease in DNA methylation levels (Cokus et al. 2008; Stroud et al. 2013). In contrast, active demethylation can specifically eliminate methylated cytosines at specific loci. Active demethylation has been observed during endosperm development and imprinting (Bauer and Fischer 2011; Choi et al. 2002; Hsieh et al. 2009; Schoft et al. 2011), gametophyte and gamete development (Park et al. 2016), tomato fruit ripening (Liu et al. 2015), and for the establishment of a successful symbiosis with *Bradyrhizobium* in Medicago (Satgé et al. 2016). Plant active DNA demethylation is catalyzed by bifunctional

enzymes, the DNA glycosylase/lyases (DNA GLs) initially identified in Arabidopsis. The Arabidopsis genome contains four genes encoding DNA GLs: *REPRESSOR OF SILENCING 1 (ROS1)*, *DEMETER (DME)*, and two *DEMETER-like (DML)* genes, *DML2* and *DML3*; (Choi et al. 2002; Gong et al. 2002; Ortega-Galisteo et al. 2008; Penterman et al. 2007). ROS1 and DME display in vitro nicking activity on methylated DNA consistent with their DNA GL activity; DNA demethylation requires cytosine removal, a process that involves the cleavage of the DNA backbone at the site of cytosine removal mediated by the AP lyase activity of ROS1 and subsequent reparation by an unknown mechanism which likely involves a putative polynucleotide kinase, a DNA polymerase, and a DNA ligase (Li et al. 2018). This results in the removal and replacement of methylated cytosines via a pathway related to base excision repair (BER; Agius et al. 2006).

Studies in Arabidopsis have suggested that multiple factors may lead the DNA demethylases to their targets (Li et al. 2018). These include ROS3 (Zheng et al. 2008), ROS4, a histone acetyltransferase, also known as IDM1 (increase in DNA methylation 1) (Qian et al. 2012), the methyl-CpG-binding protein 7 (MBD7; Lang et al. 2015), the Harbinger transposon-derived protein 1 and 2 (HDP1 and 2; Duan et al. 2017), and other partners (Li et al. 2018) that cooperate to address ROS1 to its target loci. In addition, expression of *DML* genes seems to be tightly controlled in plants. Indeed, *ROS1*, *DML2*, and *DML3* gene expressions are rather ubiquitous in Arabidopsis (Ortega-Galisteo et al. 2008; Penterman et al. 2007) as is the expression of the tomato *ROS1* orthologous genes, *SIDML1* and *SIDML2* (Liu et al. 2015). However, some of the *DML* genes display distinct patterns of expression and have been recruited for specific developmental functions. This is the case for *DEMETER (DME)* gene in Arabidopsis and related species. *DME* is specifically expressed in the central cell of the megagametophyte, which restricts DME activity to this cell type. Another example is the *SIDML2* gene that in addition of its general expression in young plant tissues

together with *SIDML1* is the only tomato *DML* gene strongly overexpressed at the onset of fruit ripening, which correlates with its role in the induction of fruit ripening (Liu et al. 2015). Recent evidence also indicates that DNA methylation levels may also participate in controlling *DML* gene expression. This was suggested following the observation that expression of the *ROS1* gene is repressed in the Arabidopsis met1 or RdDM mutants, which are characterized by a hypomethylated genome (Mathieu et al. 2007). More recently, the *ROS1* promoter was shown to contain a 39 bp DNA methylation monitoring sequence (MEMS) that acts like a “methylstat” able to sense DNA methylation level and control *ROS1* expression, thereby maintaining a dynamic balance between DNA methylation and active DNA demethylation (Lei et al. 2015; Williams et al. 2015).

9.3.2.3 DNA Methylation Distribution in Plants

The development of genome-wide strategies to analyze DNA methylation such as methylated DNA immunoprecipitation sequencing (MeDIP-seq) or whole-genome bisulfite sequencing (WGBS; Beck and Rakyán 2008; Kim et al. 2014; Yong et al. 2016) has allowed determining the distribution of DNA methylation in several eukaryotes. Among these two methods, WGBS is considered the golden standard method as it allows unraveling the position of methylated cytosines at one base resolution and therefore provides the most precise view of the distribution of 5mC in eukaryote genomes (Yong et al. 2016). In plants, the description of the genome-wide distribution of methylated cytosines was first reported in Arabidopsis (Cokus et al. 2008; Zhang et al. 2006; Zilberman et al. 2007). An increasing number of plant methylomes has now been investigated (Niederhuth et al. 2016), including crops such as rice (Li et al. 2012), maize (Eichten et al. 2013), and tomato (Zhong et al. 2013). Results indicate that DNA methylation levels vary significantly between species irrespective of the sequence contexts although in most cases similar rules seem to apply (Niederhuth et al. 2016). In plants, CG

methylation is the highest in all species tested and can vary up to threefold between species: The lowest mCG content was found in *Arabidopsis* (circa 30%; Niederhuth et al. 2016) and the highest in *Beta vulgaris* (circa 90%; Niederhuth et al. 2016). In the plant species analyzed, mCHG and mCHH contents were found at lower levels than CG methylation and ranged between 9.3 and 81.2% and between 1.4 and 18.8%, respectively, and the highest levels being found in *Beta vulgaris* in each case. The range of methylation variations in these two contexts is therefore much higher than the one observed for the CG context. When considering the distribution of mC within genomes, various studies have shown that the centromeric and peri-centromeric regions of chromosomes that are enriched in transposable elements (TEs) and tandem repeats are the most heavily methylated (Cokus et al. 2008; Lister et al. 2008; Seymour et al. 2014), although some variations between plant species were observed (Niederhuth et al. 2016). High methylation levels at TEs are consistent with 5mC being of primary importance in the control of their activity and are thought to inhibit their transcription (Cui and Cao 2014).

The distribution of DNA methylation differs in genes and TEs, and presents common features between plant species. First, early work on *Arabidopsis* showed that only 5% of the genes were methylated within their promoter region (Zhang et al. 2006). However, these studies were performed using mixture of tissues, which makes difficult to determine the precise number of genes with methylated promoters and the relation with gene expression. Since that time, other studies have analyzed organ-specific DNA methylation patterns in relation to gene expression profiles demonstrating an inverse correlation between DNA methylation in promoters and gene expression. For example, analysis of DNA methylation during soybean seed development and maturation has allowed identifying 40, 66, and 2136 genes with changes in DNA methylation levels in the CG, CHG, and CHH contexts, respectively. Most of the genes with differentially methylated regions in the CHH context showed a

negative correlation between methylation and expression levels (An et al. 2017). Similarly in tomato fruit, low methylation levels at promoters of a subset of ripening-induced genes have been correlated with gene expression (Lang et al. 2017; Liu et al. 2015; Zhong et al. 2013). Thus, promoter methylation is likely associated with the repression of gene expression although recent evidence suggests that the opposite is also possible (Lang et al. 2017).

The body of genes was also shown to be methylated, but only in the CG context, a process called gene body methylation (GbM). GbM seems conserved in plants and affects orthologous genes between species (Takuno and Gaut 2011); depletion of CHG and CHH methylation in gene bodies suggests that these two types of methylation are antagonist to transcription elongation whereas CG methylation is not (Coleman-Derr and Zilberman 2012; Feng et al. 2010; Takuno and Gaut 2011; Zemach et al. 2010; Zilberman et al. 2007). For now, the function of GbM is not understood. In *Arabidopsis*, more than 20% of the genes harbor GbM, corresponding in general to genes that are moderately expressed and constitutively active (Zhang et al. 2006; Zilberman et al. 2007). However, some plants have lost GbM methylation, suggesting it either is not required for plant viability or can be compensated by other mechanisms (Bewick and Schmitz 2017). Such situations remain rare, which suggests that GbM plays an important function in plants, still to be discovered. Interestingly, in *Arabidopsis* GbM seems to partially depend on latitude, which may reflect an adaptive function to the environment (Dubin et al. 2015). In addition to GbM, CHG and CHH methylations can also be found in the body of genes. CHG genes are usually expressed at low levels, below all genes, and those with CHH methylation, also called RdDM genes, are not expressed (Niederhuth et al. 2016; Bewick and Schmitz 2017).

The recent literature we have summarized here clearly shows that the function of DNA methylation in plants is complex and depends on both the sequence context and the localization.

9.4 Epigenetic Regulations in Fleshly Fruit

9.4.1 Evidence that HPTMs Are Essential to Fleshly Fruit Development

As mentioned above, HPTMs are critical to many plant development processes, and recent evidence indicates that these epigenetic marks are essential during fruit development and ripening (Bucher et al. 2018; Gallusci et al. 2016). Genes encoding histone deacetylases (HDACs), histone acetyltransferases (HATs), histone methyl transferases (HMTs), and histone demethylases (HDMs) have been identified in several fleshy fruit species such as apple (Janssen et al. 2008), banana (Fu et al. 2018a, b), sweet orange (Xu et al. 2015), strawberry (Gu et al. 2016), and tomato (Cigliano et al. 2013; Zhao et al. 2015). Studies have shown that some of the genes encoding histone modifiers are preferentially expressed in fruit, with stage-specific expression patterns that depend on both fruit species and HPTM modifiers. In grapevine, genome-wide analysis has revealed 33 gene-encoding proteins containing a SET domain, 10 *PRC2* genes, and 7 and 13 genes coding for putative HATs and HDAC, respectively. Some of these genes show expression patterns consistent with a possible involvement in grape berry development and ripening (Almada et al. 2011; Aquea et al. 2010; Aquea et al. 2011). Overall, these observations suggest that the corresponding proteins are recruited for the control of fruit development, ripening, and abscission in fleshy fruit species. Although not in grapevine, evidence of their role in fruit development was provided by loss and gain of function in tomato (for recent reviews: Bucher et al. 2018; Gallusci et al. 2016; Giovannoni et al. 2017).

Early studies have analyzed the tomato's high pigment mutants (*hp1*, *hp2*) which present increased carotenoid content in fruits. The corresponding tomato genes encode two subunits of an ubiquitin ligase complex, DDB1 and DET1, respectively (Tang et al. 2016b). In human, this complex is known to target histone proteins for

ubiquitination in response to DNA damages (Hu et al. 2004; Wang et al. 2006). In tomato, by impeding light signal transduction by preventing the ubiquitination of H2B histones (Benvenuto et al. 2002; Lieberman et al. 2004), these mutations may affect the transcriptional repression of genes involved in the production of carotenoids and other compound/s, therefore generating the enhanced pigmented fruit phenotype. More recently, silencing studies were conducted in tomato on different components of the histone modifier complex PRC2 (Polycomb repressive complex 2). They targeted genes encoding the enhancer of zeste EZ1 and EZ2 proteins (Bourreau et al. 2016; How Kit et al. 2010) and the FIE protein (Fertilization-Independent Endosperm Development; Liu et al. 2012). These studies revealed the roles of these genes during flower formation and early fruit development (reviewed in: Bucher et al. 2018; Gallusci et al. 2016). In a more recent work, impairment of MSI1 (multi-suppressor of IRA 1), a putative component of the tomato PRC2s, was shown to affect fruit ripening (Liu et al. 2016). However, MSI1 is also a member of the CAF-1 complex involved in chromatin assembly (Henning et al. 2005). As none of the other PRC2 components affect fruit ripening when repressed, it is possible that the effect on ripening is due to impairment of the CAF-1 complex activity rather than to the inhibition of PRC2 activity. Indeed, chromatin assembly activity might be of primary importance in tomato fruit due to the high endoreduplication level (Teyssier et al. 2008). Finally, other studies have shown that the control of histone acetylation is also important to fine-tune induction of ripening. For example, plants with reduced activity of various HDACs present delayed carotenoid accumulation and ripening (Guo et al. 2017a, b) or an opposite effect on both processes (Guo et al. 2018).

Evidence of the role of HPTMs in fruit was also provided in the frame of the fruit ENCODE project that aimed at analyzing the evolution of fleshy fruit ripening control in angiosperms. Combined genetic and epigenetic approaches were implemented on 13 different fruit species including (1) climacteric fruit species (tomato,

apple, pear, banana, melon, papaya, and peach), (2) non-climacteric fruit species (grape, strawberry, cucumber, and watermelon), and (3) dry fruit species (*Arabidopsis* and rice; Lü et al. 2018). The project generated multidimensional dataset based on transcriptomic DNA methylation and histone PTMs with a focus on H3K27me3 and H3K4me3 profiles to decipher genetic and epigenetic events controlling fruit ripening (Lü et al. 2018). In this context, researchers focused on key molecular players involved in ethylene-dependent ripening circuits in climacteric fruit and their orthologues in non-climacteric and dry fruit. Although global- and locus-specific DNA methylation changes were observed in all fruit species during ripening induction, DNA demethylation was suggested to be only required for tomato ripening. However, these conclusions were based on correlative studies without functional foundation and are not consistent with the recent demonstration that in addition to tomato fruit ripening (see below; Lang et al. 2017; Liu et al. 2015), strawberry fruit ripening and sweet orange fruit ripening are also under DNA methylation control although different mechanisms are operating (Cheng et al. 2018a; Huang et al. 2019). In contrast, Lü et al. (2018) suggested that, instead of DNA methylation, the repressive mark H3K27me3 may play a conserved—and maybe central—role in regulating fruit ripening, although its precise function and importance may vary between fruit species. Indeed, for a few ripening-related genes, a correlation was found between their induction during ripening and the removal of H3K27me3 in several fruit species, therefore suggesting an ancestral inherited role for this mark in angiosperm fruit ripening (Lü et al. 2018). Interestingly, a recent study indicates that H3K27me3 may be involved in the control of methoxypyrazines (MPs) accumulation in grape berries, a compound known to contribute to the herbaceous characters in wine (Battilana et al. 2017). MPs biosynthesis depends on the expression of the *VvOMT3* gene which encodes a protein controlling the final and key step of this biosynthetic pathway in grape. However, MP accumulation is variety dependent. For example, berries from

Cabernet Sauvignon accumulate MPs, but those of the Pinot Meunier-derived dwarf do not. A recent study has shown the mark H3K27me3 is abundant at the *VvOMT3* locus in Pinot Meunier dwarf but not in Cabernet Sauvignon berries (Battilana et al. 2017), suggesting that H3K27me3 inhibits *VvOMT3* gene expression resulting in the inhibition of MP biosynthesis. Although these results are consistent with an important role of H3K27me3 in fruit ripening control, this mark does not seem to be critical for ripening in all fleshy fruit species shown in tomato (Boureau et al. 2016; How Kit et al. 2010; Liu et al. 2012).

The characterization of PRC2 mutants or of mutants affected in the removal of the H3K27me3 mark will now be necessary to better assess the importance of this epigenetic mark in modulating the epigenetic landscape and its consequences on gene expression and fruit phenotypes

9.4.2 DNA Methylation Role in Fruit Development and Shape

So far, very few studies have investigated the possible role of epigenetic mechanisms in the control of organogenesis and early development of fruit. However, a few examples show that DNA methylation is likely part of the regulatory networks that control fruit shape and size. One recent example is provided by the analysis of the mantled phenotype in oil palm (*Elaeis guineensis*) that was identified in plants generated by somatic embryogenesis (Rival et al. 1998). Oil palm plants with the mantled phenotype are characterized by the development of flowers with carpeloid structures in place of male organs leading to the formation of a fruit with various phenotypes ranging from normal-looking fruits to very small fruits (Dussert et al. 2000). This phenotype was recently shown to be caused by the hypo-methylation of a Karma-like LINE retrotransposon located within an intron of the *DEFICIENS* (*DEF*) gene. Normal fruits develop when the Karma retrotransposon is methylated, whereas its hypo-methylation leads to the mantled phenotype due to the inhibition of *DEF*

splicing (Ong-Abdullah et al. 2015). For tomato, impairing DNA demethylases does not only inhibit ripening (see Sect. 9.4.2.1), but also alter flower and fruit shape. In particular, fruit presented a significant increase in the number of locules that resulted from an increased number of carpels formed during flower development (Liu et al. 2015). However, it is still unclear whether this effect is a direct or indirect consequence of a deficient demethylation process.

A final example comes from the analysis of apple fruit development using two double haploid apple varieties with fruit, whose size correlates with the number of cells in the fruit (Daccord et al. 2017). While these two varieties have genomes that only differ by a limited number of single-nucleotide polymorphisms (SNPs), 294 differentially methylated regions (DMRs) were identified in proximity to genes that could be involved in fruit growth and development. The causal relationship between these DMRs and difference in fruit size is still elusive (Daccord et al. 2017).

9.4.2.1 Evidence that DNA Methylation Is Critical to Fruit Ripening

DNA methylation changes were first documented in tomato decades ago by Hadfield et al. (1993), who showed that genes induced at the onset of fruit ripening had changes in their methylation state. Since that time, the description of the *Colorless Non-Ripening* (*Cnr*) epimutation provided compelling evidence that DNA methylation control is essential to fruit ripening (Manning et al. 2006). Fruits of the *Cnr* epimutant are characterized by a severe reduction in ethylene production, an inhibition of fruit softening, and a lack of carotenoid synthesis and accumulation (Thompson et al. 1999). The *Cnr* epimutant phenotype is very stable, and reverting sectors were only observed on 3 individual fruits on independent plants from more than 3000 plants. This allowed the positional cloning of the *CNR* locus that was shown to contain only one gene differentially regulated between *Cnr* and WT fruits, yet without any sequence differences between both genetic backgrounds (Manning et al. 2006). This gene, which encodes a

SQUAMOSA promoter-binding protein-like (SBP-box/SPL) transcription factor, presented a 286-bp-long hyper-methylated region located 2.3 kb upstream of the TSS. Hyper-methylation was only found in the *Cnr* background and resulted in *CNR* gene repression and blocking of fruit ripening (Manning et al. 2006). Additional evidence that methylation upstream of the promoter was responsible for the repression of the *CNR* gene was provided using virus-induced gene silencing (VIGS) to repress the expression of the tomato *CMT3* gene in the *Cnr* background that allowed reversing the *Cnr* phenotype to WT, whereas the same approach using *MET1* or the *DRM* genes had much weaker effects (Chen et al. 2015). This approach was sufficient to reduce methylation at the CHG sites located in the hyper-methylated 286-bp region of the *CNR* promoter and to increase the expression of *CNR* indicating that the methylation of *CNR* gene in the *Cnr* background requires the functional maintenance of methylation machinery. Hence, maintenance of methylation at the *Cnr* locus is necessary for the somatic stability of the epimutation (Chen et al. 2015). Since the description of *Cnr*, other studies have led to the identification of epialleles in tomato. They include the demonstration that variations in vitamin E content of tomato fruit are determined in part by the methylation level of the promoter region of *VTE3*, a gene which encodes a 2-methyl-6-phytylquinol methyltransferase, responsible for an essential step in tocopherol biosynthesis (Quadrana et al. 2014). Methylation variations were observed between tomato accessions that were correlated with changes in *VTE3* gene expression and fruit vitamin E content. Additional epialleles were also identified in the progeny of crossings between M82, a commercial tomato accession, and *Solanum penellii*, a wild tomato relative (Gouil and Baulcombe 2018). However, the stability of the newly generated epialleles was not established in this case. Epialleles that determine the color of the skin were also found in apple and pear (El-Sharkawy et al. 2015; Telias et al. 2011; Wang et al. 2013). In both cases, hyper-methylation of the promoter region of *MYB10* was associated with repression of the gene and of anthocyanin biosynthesis in the skin.

9.4.2.2 DNA Methylation Reprogramming in Fleshy Fruit

Analysis of the global DNA methylation level at different stages of tomato fruit development indicated that the total content in 5mC decreased in the pericarp of tomato fruit from 29.9% at the breaker stage to 20.1% at the red ripe stage (Teyssier et al. 2008). This decrease in DNA methylation level was confirmed by WGBS of the tomato fruit genomic DNA at four developmental stages, namely immature green, breaker, turning, and fully ripe fruit of WT plants and also at two stages in the *Cnr* and *ripening inhibitor (rin)* mutant genetic backgrounds, both impaired in the ripening process (Zhong et al. 2013). Results indicated that in addition to a decrease in methylation level at CG sites observed in TE-rich regions, DNA methylation was also reduced at the promoters of genes that are induced during fruit ripening, including gene-encoding proteins with important role in this process, such as the *CNR*, the *RIN*, or the *NOR* genes (Reviewed in: Bucher et al. 2018; Gallusci et al. 2016; Giovannoni et al. 2017). Noteworthy, CHH methylation is high in tomato (11% in ripe fruit, 13% in non-ripe fruit, and 8.3% in leaves; Zhong et al. 2013) as compared to previously described CHH methylation levels in *Arabidopsis* (1.5%; Cokus et al. 2008) and in other plants (Niederhuth et al. 2016), and was found higher in fruit (Zhong et al. 2013).

With the aim to investigate the mechanisms underlying the loss of genomic DNA methylation occurring at the onset of fruit ripening, Liu et al. (2015) have identified four tomato genes encoding putative DNA demethylase. One of them, *SIDML2*, was strongly upregulated at the onset of ripening, simultaneously to the decrease in DNA methylation. Inhibition of *SIDML2* gene expression using RNAi and VIGS strategies (Liu et al. 2015) or by CRISPR-Cas9-mediated mutagenesis (Lang et al. 2017) indicated that *SIDML2* is an absolute requirement for tomato fruit ripening to occur. Ripening inhibition was associated with the repression of genes encoding the *RIN*, *NOR*, and *CNR* transcription factors that play a major role in the induction of tomato fruit

ripening (Lang et al. 2017; Liu et al. 2015). Of note, the promoter region of these transcription factors is normally demethylated during fruit ripening, whereas loss of *SIDML2* function was associated with the absence of demethylation and gene repression. A similar situation was observed at 600 ripening-induced genes that failed to be expressed and remained hyper-methylated in their promoter region. Interestingly, 598 other hyper-methylated genes normally repressed during the ripening of wild-type tomato fruit maintained their expression level in the mutant background (Lang et al. 2017), suggesting that DNA methylation is also associated with gene expression in tomato fruit.

It was recently suggested in the frame of a fruit ENCODE project that DNA demethylation might not be a general process controlling fleshy fruit ripening and dry fruit maturation, in contrast to H3K27me3 (Lü et al. 2018). However, recent works indicate that DNA methylation control is likely important in other fruits as well. The description of the strawberry fruit methylome indicates that fruit genomic DNA becomes massively demethylated during the ripening process (Cheng et al. 2018b), as observed in tomato (Teyssier et al. 2008; Zhong et al. 2013). Demethylated regions were enriched at a large subset of genes induced during ripening suggesting a direct link with the expression of ripening-induced genes, consistent with the demonstration that the treatment of strawberry fruit with a demethylating agent accelerates fruit ripening (Cheng et al. 2018b). Interestingly, in strawberry, no demethylase-encoding gene could be identified that was involved in the loss of methylation. Decrease in methylation was rather associated with repression of the RdDM pathway that could in turn lead to demethylation at specific loci (Cheng et al. 2018b). In a more recent study, Huang et al. (2019) analyzed the changes in genomic DNA methylation in the skin of orange fruit and demonstrated a general increase in DNA methylation along with fruit development and ripening. Inhibition of methylation by means of azacytidine, a demethylating agent, resulted in delayed ripening indicating that increase in DNA methylation is necessary for

orange fruit ripening to occur (Huang et al. 2019). Taken together, these results highlight the general importance of DNA methylation control in fleshy fruit, even though it becomes clear that a diversity of mechanisms is operating depending on the plant species under study (Fig. 9.3).

9.5 Interaction Between Hormones and Epigenetic Regulations in Fleshy Fruit Development and Ripening

Other important regulatory pathways, including hormones and transcription factors, control fruit ripening. Their complex interactions with chromatin-based regulations need to be investigated. Several recent works have illustrated that hormone signaling may involve an epigenetic component (Yamamuro et al. 2016), but very few studies have addressed this question in fruit so far (Lü et al. 2018; Zuo et al. 2018).

Fruit set is known to be under hormonal control, and a diversity of hormones plays a critical role in this process (see Chap. 12). They include auxins, gibberellic acids, or cytokinins that can promote parthenocarpic fruit development when applied alone, although their combined action appears much more efficient in both dry and fleshy fruits (for recent reviews: Joldersma and Liu 2018; Kumar et al. 2014). The involvement of epigenetic regulation during this developmental phase is still poorly studied. At present, evidence is mounting that PRC2 complexes might be involved in this process as illustrated by the elongation of fruit in the absence of fertilization in Arabidopsis PRC2 mutants (Goodrich et al. 1997) and parthenocarpic in tomato (Liu et al. 2012). However, it is not clear whether PRC2s control fruit elongation directly or through auxin signaling. Consistent with the latter, it has been shown that genes involved in auxin biosynthesis or signaling are enriched in the H3K27me3 repressive mark, which is established by PRC2s (Lafos et al. 2011). In addition, *met1* mutants show an elongation of fruit without pollination, suggesting that maintenance of DNA methylation is

necessary to prevent fruit development in the absence of fertilization (FitzGerald et al. 2008). In this case, interaction with hormonal regulations has not been yet investigated, even though interplay between PRC2 and DNA methylations has been suggested in the megagametophyte of Arabidopsis developing flowers. Therefore, auxins, DNA methylation, and histone marks could control the induction of seed and fruit development in a coordinate manner.

The role of hormones varies between fruit types, with ethylene being the major player in climacteric fruit, whereas ABA appears to have a more prominent role in non-climacteric fruit (McAtee et al. 2013) including grapevine (Fortes et al. 2015). Yet, the relationship between hormonal and epigenetic regulations in fruit ripening control is still poorly understood. As far as histone PTMs are concerned, a recent study performed in banana has shown that the ethylene response factor11 (MaERF11), a negative regulator of banana fruit ripening, may recruit the MaHDA1 HDAC at the promoters of the *MaEXP2*, *MaEXP7*, *MaEXP8*, and *MaACO1* genes in immature green fruit (Han et al. 2016). This would result in deacetylation and repression of these genes, before ripening induction, an effect that would be relieved by the massive synthesis of ethylene occurring at the onset of ripening (Han et al. 2016). HDACs were also suggested to interact with ethylene to regulate gene expression involved in longan fruit senescence (Kuang et al. 2011). There is, however, stronger evidence that ethylene and DNA methylation interact to control fruit ripening, at least in the tomato (Liu et al. 2015), where genes involved in ethylene biosynthesis are misregulated in *Sldml2* mutants (Lang et al. 2017). Inversely, tomato plants affected in ethylene signal transduction were shown to have deeply modified fruit methylation patterns, consistent with a loop regulation between DNA methylation/demethylation and ethylene biosynthesis in tomato fruit (Zuo et al. 2018).

ABA is thought to play a much more prominent role in the control of ripening of non-climacteric fruit (McAtee et al. 2013). In strawberry, some of the ABA biosynthetic genes

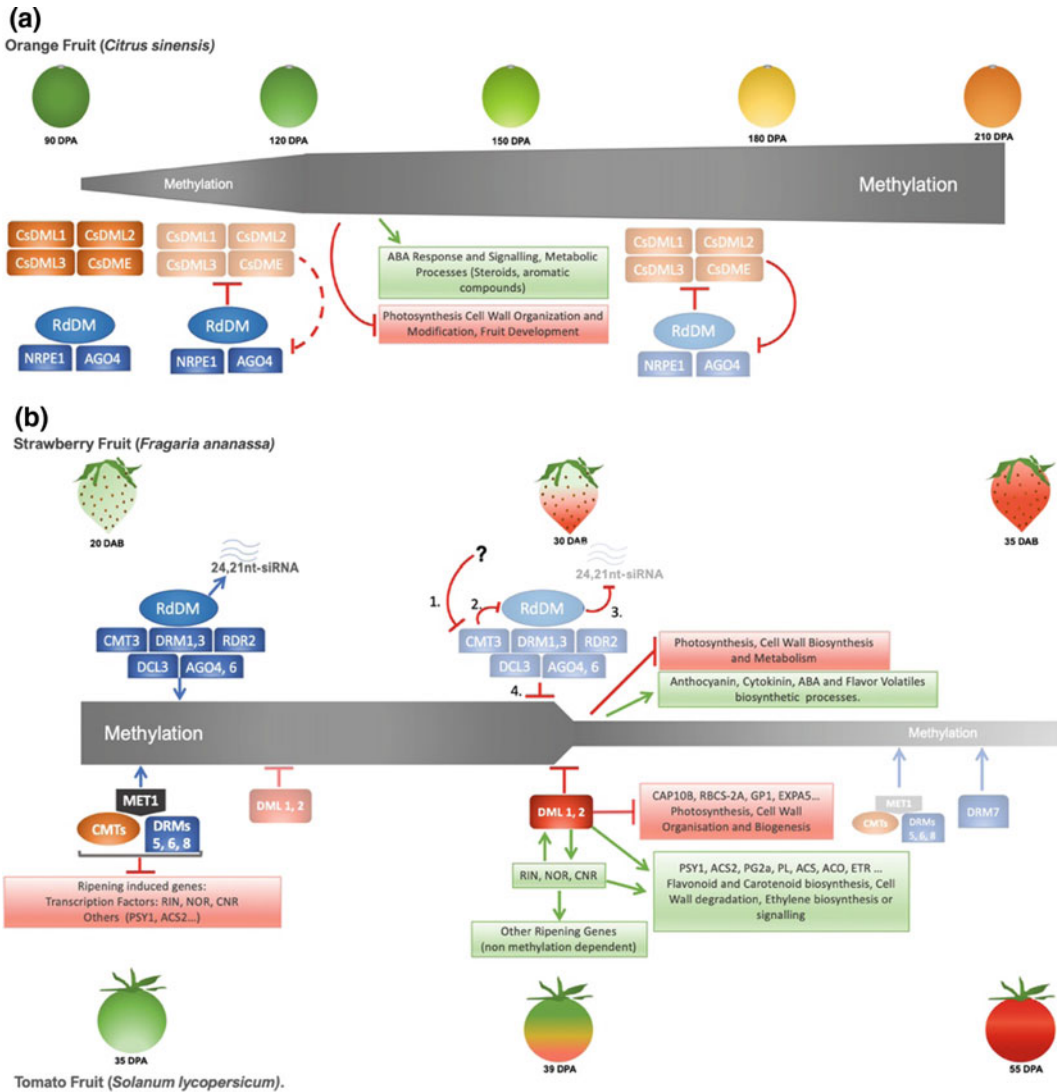


Fig. 9.3 Putative roles of genomic DNA methylation in fleshy fruit. **a** Function of DNA methylation in sweet orange fruit: Genomic DNA methylation increases from 13% of total cytosine in 90 dpa old sweet orange fruit to 14.5% in 210 DPA old fruit. Increase in DNA methylation is correlated with the gradual decrease in the expression of DNA demethylase (DML) genes and of genes involved in the RNA-directed DNA methylation pathway (*NRPE1*, *AGO4*). Ripening-associated hyper-methylated regions were associated with hundreds of genes normally expressed at early stages of fruit development, as those involved in photosynthesis, but also with the induction of several genes involved in orange fruit ripening. Results suggest that DNA methylation is critical to ripening of sweet orange fruit, as confirmed by the ripening inhibitory effect of azacytidine, an inhibitor of genomic DNA methylation. Up- and down-regulated processes shown in the figure are, respectively, associated with DEGs correlated with hyper-DMR (gain of methylation during

ripening). **b** Function of DNA demethylation in strawberry fruit and in tomato fruit: genomic DNA methylation in young strawberry immature fruit is 7.5% and decreases during fruit ripening. Loss of methylation occurs at genes involved in the ripening process (anthocyanin accumulation, secondary compound synthesis, etc.), suggesting that demethylation is necessary for ripening induction. Consistent with this view, fruit treatment with azacytidine results in early ripening. Reduction of methylation was correlated with the reduction of the expression of genes involved in the RdDM pathway and with reduced accumulation of short interfering RNAs of 24 nt. In contrast, DNA demethylase-encoding genes are not induced. Genomic DNA methylation decreases from 30% of total cytosine in young immature fruit to 20% in red ripe fruit (Teyssier et al. 2008). Decrease in DNA methylation correlates with up-regulation of *SIDML2*, one of the tomato DNA demethylases. Genes encoding RIN, NOR, CNR transcription factors that control fruit ripening

and other genes encoding enzymes necessary to ripening (phytoene synthase 1, polygalacturonase, etc.) have hyper-methylated promoters and are repressed in immature green tomato fruit (Lang et al. 2017; Liu et al. 2015). Some of the genes involved in photosynthesis are expressed in young fruit even though their promoter is methylated at this stage (Lang et al. 2017). Reduction of DNA methylation that occurs at the onset of fruit ripening necessitates the expression of the *SIDML2* gene (Liu et al. 2015) and correlates with the reduced expression of genes involved in maintenance of DNA methylation (Teyssier et al. 2008). Demethylation occurs in the promoter region of many of the genes encoding the CNR, RIN, and NOR transcription factors, as well as of genes involved in carotenoid (phytoene synthase 1), ethylene synthesis (ACC synthase

2), and cell wall metabolism (polygalacturonase, etc.), among others, and is associated with their expression and fruit ripening (Lang et al. 2017; Liu et al. 2015). For some genes (*CAP10*, *RBCS*, etc.) demethylation was correlated with gene repression (Lang et al. 2017). SIMET1 (cytosine DNA methyltransferase 1), CMT (chromomethylase), DRM (domain, rearranged methyltransferase), DML (DEMETER-like demethylase), PSY1 (phytoene synthase 1), ACS2 (ACC synthase 2), RIN (ripening inhibitor), NOR (non-ripening), CNR (colorless non-ripening). Genes in boxes with intense colors (orange, blue, or gray) are strongly expressed. Those in boxes with pale colors are weakly expressed. Green arrows indicate activation, and red bars repression. Repressed processes and genes are indicated in red, and those activated in green

are hypomethylated in their promoter region and present an enhanced expression during ripening (Cheng et al. 2018b). However, there is no evidence of a causal interaction between ABA synthesis and transduction signal and variations in DNA methylation at these genes.

9.6 Conclusions: Specific Aspect of Epigenetic Regulations in Grapevine

The importance of epigenetic regulations has been demonstrated in Arabidopsis, for which a plethora of mutants have been generated that affect the regulation of DNA methylation and histone PTMs and were used to illustrate the prominent roles of epigenetic regulations in plant development and adaptation to stresses. However, it is becoming clear that although epigenetic mechanisms have been conserved within the plant kingdom, they have been recruited for a diversity of developmental processes that may vary between species. In addition, different epigenetic mechanisms may fulfill similar physiological functions in different plants. An example is provided by the function of the DNA demethylase *SIDML2* that mediates the active demethylation of tomato fruit genomic DNA, a process necessary to tomato fruit ripening (Liu et al. 2015), whereas in strawberry ripening specific DNA demethylation is controlled by inhibition of de novo methylation through the RdDM pathway (Cheng et al. 2018b), and in some other cases such as sweet orange there is no

massive demethylation during fruit ripening (Huang et al. 2019).

Noteworthy, recent works also indicate that epigenetic regulations may have much stronger impacts on plant phenotypes and gene expression in crops than in the model plant Arabidopsis (Gallusci et al. 2016; Mirouze and Vitte 2014). A diversity of reasons may contribute to this observation including the lower methylation level and transposon content of Arabidopsis as compared to most crops (Lee and Kim 2014), and differences in genome organization, for example the distance between genes and transposons (Niederhuth et al. 2016). Genome analysis has shown that the grapevine contains more transposons than Arabidopsis (Jaillon et al. 2007). The most striking difference between the two species is the alternation in grapevines of regions with high and low gene density along chromosomes, together with the high density of transposons nearby genes and within introns. In addition to possible impact on gene expression, higher transposon density increases the probability that their mobility will generate variants due to loss of gene function. Indeed, genetic variations due to transposons that are inserted within or in the vicinity of genes have been described in grape and other plants (Hirsch and Springer 2017; Lijavetzky et al. 2006; This et al. 2007; Verriès et al. 2000). The most striking example is the white color of grape berries that has been shown due to the insertion of the *GRETI* transposon in the promoter region of *MybA1* in berry skin cells (Kobayashi et al. 2004;

Lijavetzky et al. 2006). Hence, the control of transposon mobility is likely to be an important issue in grapevine even more because it is a perennial plant that is clonally propagated, which allows maintaining somatic variations in a population.

As far as fruit is concerned, several studies have already highlighted the relevance of epigenetic regulations in fruit crops. Whereas DNA methylation was shown to play important roles in tomato, strawberry, and orange fruit during ripening (Cheng et al. 2018b; Huang et al. 2019; Liu et al. 2015), histone PTMs are also likely important at various phases of fleshy fruit development (Gallusci et al. 2016; Lü et al. 2018). So far, evidence of the role of both types of epigenetic marks in grape berries, and in many other fruit crops, awaits demonstration. The combination of high-throughput sequencing associated with chromatin immunoprecipitation or with bisulfite treatment of DNA will undoubtedly shed light on the dynamics of epigenetic marks in fruit, as illustrated in the fruit ENCODE project (Lü et al. 2018), but such approaches remain correlative in nature and will require to be completed by functional analysis of the corresponding genes. In grapevine, generation of loss of function variants is hampered by the difficulty to generate RNAi lines and CRISPR-Cas9 mutations due to the limited efficiency of plant transformation/regeneration processes (see Chap. 16). So far, *in silico* analyses, conducted on grapevine, have identified candidate genes involved in the control of epigenetic marks (see Sect. 9.4.1). Many of these genes are differentially expressed in grape berries (Almada et al. 2011; Aquea et al. 2010, 2011), suggesting that histone PTMs—and more globally, chromatin remodeling—could play a key role in grapefruit development and ripening. However, ChIP analysis would be necessary to determine the variations of histone mark distribution. Similarly, expression analysis of genes involved in the control of DNA methylation associated with the genome-wide description of DNA methylation changes would be necessary to assess the potential role of DNA methylation in fruit. Noteworthy, given the clear metabolic

differences observed between the skin and the pulp, such studies should be performed in each tissue separately. The final demonstration of the role of epigenetic marks in grape berries will require studying the effects of mutations affecting genes that encode histone writers and erasers, as well as enzymes involved in DNA methylation control. Pharmacological approaches using specific drugs interfering with these epigenetic processes could also provide alternative strategies to study the function of epigenetic marks in grape berries (Baubec et al. 2009; Finnegan et al. 2018; Griffin et al. 2016).

In addition to the specificity of grape berry development and ripening, grapevine development and propagation strategies present features that may emphasize the impact of epigenetic regulations on plant phenotypes. First, grapevine is a clonally propagated plant, which contributes to limit its genetic diversity and subsequent phenotypic variations, although both human selection and naturally occurring mutations contribute to the phenotypic diversity (Ferreira et al. 2018). As far as natural clonal propagation is concerned, epigenetic processes are likely contributing to the adaptation of plants to their local environment and may provide selective advantage (Verhoeven and Preite 2014). In line with this idea, a recent study has shown that plants of the mangrove species *Laguncularia racemosa*, have little genetic differences, but possess important DNA methylation differences, suggesting that epigenetic variation in natural plant populations may have an important role in the adaptation to different environments (Lira-Medeiros et al. 2010). Additional evidence of the role of epigenetic processes in clonally propagated plants is provided by the analysis of the transgenerational memory of stresses in white clover (González et al. 2016, 2018). Results indicate that among the various stresses applied to the parental plants, drought-generated transgenerational effects in clonally propagated offspring were transmitted concomitantly to DNA methylation changes and maintained during several clonal offspring generations. So far, there was no causal relationship demonstrated between DNA methylation changes and transgenerational

effects in these studies, but results suggest a possible link between both types of event. As far as grape is concerned, such studies have not been performed and it is unknown whether genetically identical clones may be epigenetically different.

In addition, clones of the same origin may become with time epigenetically different. Indeed, environmental conditions do impact the epigenetic status of plants as epigenetic mechanisms are essential to plant responses to both non-biotic and biotic stresses (Gutzat and Scheid 2012; Kinoshita and Seki 2014; Lämke and Bäurle 2017). However, the stability and maintenance of stress-induced epigenetic modifications have been a matter for debate in annual plants (Crisp et al. 2016). As far as perennial plants are concerned, new epigenetic imprints generated by environmental conditions could accumulate over the years and be maintained in the meristem, thereby generating specific epigenetic status for the plants depending on their location and environment (Lafon-Placette et al. 2018; Raj et al. 2011). Hence, genetically identical clones could become epigenetically distinct based on their growing location. The recent demonstration of important changes in methylation patterns that seem to depend on the grapevine growing region is consistent with this idea, although clones of the same origin were not used in this study (Xie et al. 2017).

In addition to stresses (Fortes and Gallusci 2017), climate changes have important consequences on grapevine phenology: it has been shown that timing of budburst and flowering as well as fruit quality are impacted by global warming (Van Leeuwen and Darriet 2016). The relevance of epigenetic-based processes involved in the adaptation of grape plants to these environmental constraints is so far unclear. However, budburst was shown to be under methylation control in poplar, active demethylation being involved in the induction of bud opening after winter (Conde et al. 2017). Whether epigenetic mechanisms exist in grapevines that control budburst is still unknown, recent studies have suggested that PcG proteins might be involved in the control of bud break and flowering (Almada et al. 2011), a function that would be reminiscent

to the epigenetic control of vernalization in *Arabidopsis*. Indeed, a better understanding of the role of chromatin-based regulations in the control of developmental stages during the annual life cycle of grape may provide new strategies to modify grapevine phenology and improve adaptation of this important fruit crop to climate changes.

A very important additional specific feature that differentiates grapevines from other plants is that since the second half of the nineteenth century, grapevines are mostly grown grafted on rootstocks, to protect the plant from *Phylloxera* and other soilborne pests and diseases (Ollat et al. 2017; see Chap. 14). Grafting does not correspond to the simple juxtaposition of two organisms: the two associated graft partners, rootstock and scion, actively interact with each other. Hence, grafting is known to induce phenotypic changes in the scion and in the rootstock and to improve scion growth potential and fruit yield and quality (Albacete et al. 2015; Kyriacou et al. 2017; Warschefsky et al. 2016). Hetero-grafting (association of a scion and a rootstock with different genotypes) was shown in some cases to generate inheritable sporadic phenotypic changes in the scion, affecting diverse developmental processes including fruit growth and ripening (Hirata 1980; Taller et al. 1998; Yagishita 1961). Although the molecular bases for graft-dependent phenotypic variations are obviously multiple including hormonal, proteins, and mRNA exchange (Albacete et al. 2015; Gregory et al. 2013; Ollat et al. 2017), recent data suggest that epigenetic mechanisms could be among them (Berger et al. 2018). Indeed, several reports indicate that hetero-grafting induces changes in DNA methylation patterns in the scion in different species including *Arabidopsis* (Lewsey et al. 2016), *Hevea* (Uthup et al. 2018), solanaceous (Wu et al. 2013), and cucurbitaceous (Avramidou et al. 2015; Xanthopoulou et al. 2019) crops. Moreover, part of these modifications was shown to be inheritable (Wu et al. 2013). These epigenetic changes could induce phenotypic variations, although no example of such functional relationship has been demonstrated yet. Interestingly, mechanistic studies performed in *Arabidopsis* and in different *Solanaceae* species have revealed a

molecular mechanism which is responsible for the production of epi-variants in grafted plants: small RNAs produced in the scion can induce de novo methylation in the rootstock (Bai et al. 2011; Kasai et al. 2016; Melnyk et al. 2011) and vice versa (Bai et al. 2011). Such epigenetic modifications were shown to occur at loci with homologous sequences to the exchanged small RNAs. When these loci correspond to gene regulatory regions, they can impact gene expression, hence plant phenotype. Whether such graft-dependent mechanisms also exist in grapevine and could generate stable phenotypic diversity remains to be determined. As a conclusion, whereas genetics is a driving force in shaping the phenotypic diversity of grape plants, epigenetics is likely providing an additional layer of variability that could impact grape development and adaptation to environment, and generate stable phenotypical variants.

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