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REVIEW PAPER

Epigenetic control of plant senescence and linked processes

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Abstract

Senescence processes are part of the plant developmental programme. They involve reprogramming of gene expression and are under the control of a complex regulatory network closely linked to other developmental and stress-responsive pathways. Recent evidence indicates that leaf senescence is regulated via epigenetic mechanisms. In the present review, the epigenetic control of plant senescence is discussed in the broader context of environment-sensitive plant development. The review outlines the concept of epigenetic control of interconnected regulatory pathways steering stress responses and plant development. Besides giving an overview of techniques used in the field, it summarizes recent findings on global alterations in chromatin structure, histone and DNA modifications, and ATP-dependent chromatin remodelling during plant senescence and linked processes.

Key words: *Arabidopsis*, ATP-dependent chromatin remodelling, chromatin alterations, DNA methylation, leaf senescence, histone modifications, stress.

Senescence, an important period of plant development

Starting from one cell, the zygote, plants develop to multicellular, structured, and complex organisms, highly efficient to survive in an ever-changing environment. Plant development is driven by cell division and cell differentiation. Major steps in the developmental programme are embryogenesis, seed development, and vegetative growth, including the formation of photosynthetically active leaves and flowering. The developmental programme is highly flexible, responding to internal and external signals, including biotic and abiotic stressors. However, whole-plant development does not imply simply the formation of new cells, cell layers and organs; it also includes degradation and death of cells. Since this is also included in the developmental programme, it can be named 'programmed cell death'. The most striking developmental programme, ending with cell death, is leaf senescence, being responsible for the annual colouring of leaves in autumn and also being responsible for efficient recycling of resources in our crop plants needed for high yield.

Leaf senescence is under the control of, and is linked to, different regulatory pathways

A major developmental step like senescence has to be under the control of a complex regulatory network where internal and external signals are fed in. On the one hand, the senescence programme has to be coordinated with whole-plant development. In particular, the switch from vegetative to generative growth on the whole-plant level is often tightly linked to the senescence programme. This enables a concerted interplay and finally maximizes generative fitness. Therefore, signalling pathways steering flowering are connected to the senescence regulatory pathway. On the other hand, plant`s environment is dynamically changing, and to survive under these

Abbreviations: ABA, abscisic acid; ChIP, chromatin immunoprecipitation; ChIP-seq, ChIP-sequencing; ERF, ethylene response factor; HDA, histone deacetylase; HMT, histone methyltransferase; ncRNA, non-coding RNA; PR, pathogenesis-related; SA, salicylic acid; SAG, senescence-associated gene; SDG, senescence downregulated gene; TE, transposable element;TF, transcription factor.

conditions, plants have to adapt to the changed environment. Leaf senescence can be triggered and modulated by different environmental conditions, and the senescence programme and signalling pathways of abiotic and biotic stress responses are closely linked. The sophisticated interplay between these pathways enables modulation and fine-tuning of the developmental senescence programme in response to environmental conditions. Premature leaf senescence under stress is, in a way, an emergency programme that saves resources for the growing seeds to ensure reproduction even under these life-threatening conditions.

Phytohormones play an important role as upstream regulators in this interconnected regulatory network of development and stress responses. In recent years, it has become obvious that phytohormones act in a very complex network and normally do not operate independently from the other hormones and that they have multiple effects interconnecting different signalling pathways (Gepstein and Glick, 2013; Jibran *et al.*, 2013). Further downstream, the developmental programme and stress responses are realized by differential expression of genes encoding either regulatory components or proteins executing the programmes. Differential gene expression as a central process converting upstream signals into a response is the main target of regulation.

Regulation of gene expression by *trans*-acting factors during developmental and stress-induced senescence

Gene expression is under the control of different interrelated mechanisms: on the one hand, the interaction of transcription factors (TFs) and *cis*-regulatory DNA elements, and on the other hand, alterations in higher-order chromatin structure related to modifications of DNA sectors and associated histones (see next section).

Proteins, binding to specific DNA sequences in the promoters of genes, are the most prominent regulators of spatial and temporal gene expression. A plethora of such TFs, *trans*-acting on *cis*-elements of DNA, is known. Leaf senescence as a major developmental step involves massive reprogramming of gene expression. Genes upregulated during senescence are termed SAGs (senescence-associated genes), and genes downregulated during senescence SDGs (senescence downregulated genes). Several transcriptome analyses focusing on developmental and also stress-induced senescence have been performed (Buchanan-Wollaston *et al.*, 2005; van der Graaff *et al.*, 2006; Breeze *et al.*, 2011; Guo and Gan, 2012) revealing specific classes of senescence-regulated genes. While many genes related to photosynthesis and other metabolic processes of mature leaves are downregulated, other classes of genes, such as genes involved in degradation of proteins and lipids and genes protecting the chloroplast during its dismantling, are upregulated. Also, many regulatory genes are expressed in a senescence-specific manner, indicating their involvement in the regulatory network of leaf senescence. In particular, TFs of the AP2–EREBP, bZIP, C3H, CCAAT–DR1, CCAAT–HAP2, NAC, and WRKY families have been found to be regulated during senescence (Lim *et al.*, 2007*b*; Balazadeh *et al.*, 2008; Breeze *et al.*, 2011; Ay *et al.*, 2014). These transcriptome analyses also show that parts of the senescence regulatory pathway act during developmental as well as during stress-induced senescence, while others are more specific. A comparative analysis of gene expression profiles among 27 different treatments known to promote senescence-like processes, such as phytohormone treatments, shading, biotic stress like pathogenic infections with *Botrytis cinerea*, and abiotic stresses like drought stress or high glucose/low nitrogen, with that of developmental leaf senescence was performed by Guo and Gan (2012). This analysis showed that the expression profiles of the individual treatments overlapped to various extents with developmental leaf senescence. These authors showed that, early pathways in particular for the induction of leaf senescence differed but later converged into a shared senescence programme (Guo and Gan, 2012). Recent findings show that, in addition to the senescence-specific regulation of gene expression by TFs, leaf senescence is also controlled by another, higher-order regulatory mechanism operating via differential alterations of chromatin structure at distinct gene loci (Humbeck, 2013).

Regulation of gene expression by dynamic alterations in chromatin structure during senescence and related developmental and stress conditions

The eukaryotic nuclear DNA is associated with proteins and undergoes hierarchical folding. The basic structure of this DNA–protein complex, so-called chromatin, is the nucleosome, consisting of a histone octamer, usually formed by two molecules of each of the histone proteins H2A, H2B, H3, and H4, and about 146 bp of DNA wrapped around the histones. Neighbouring nucleosome core particles are connected by a link of 15–55 bp of DNA, which is associated with the linker histone H1 (Luger *et al.*, 1997). This structure is the basis of the chromatin in eukaryotic nuclei formed by three-dimensional packaging of DNA and histone proteins in eukaryotic nuclei. The nucleosomes in interphase nuclei can be arranged in a more dense type of packaging (heterochromatin) and a more open type (euchromatin). Dense heterochromatin disables access of TFs and RNA polymerase II machinery, and thereby represses transcriptional activity. On the other hand, open euchromatin is accessible for these proteins, enabling transcription. The structure of chromatin is not fixed. During development and in response to stress, it can alter in a very dynamic way, thereby controlling expression of associated genes. In recent years, many factors that are responsible for these dynamic alterations in chromatin structure have been identified. In the following sections, we first discuss recent findings on global changes in chromatin structure and then in more detail outline our present understanding of the distinct but interconnected epigenetic mechanisms underlying locus-specific alterations in chromatin structure, focusing on senescence and related developmental and stress conditions.

In addition, we summarize the *status quo* methods used in the modern field of chromatin structure analysis (Table 1).

Global alterations in interphase nuclei occur throughout plant development and under different stress conditions

Immunodecoration of epigenetic marks by specific antibodies (immunocytochemistry) or labelling of DNA via fluorescence *in situ* hybridization allows a global view on chromatin structure in nuclei of developing or stressed plants. Using these techniques (Table 1) several authors have reported that chromatin structure plays a pivotal role in many aspects of plant development, including senescence (Li *et al.*, 2002; Berger and Gaudin, 2003; Ay *et al.*, 2009). In addition, mutants that are defective in chromatin dynamics show abnormalities at multiple developmental stages (Exner *et al.*, 2006). For example, Tessadori *et al.* (2007) observed a drastic transient decondensation of pericentromeric and gene-rich chromatin in leaf mesophyll interphase nuclei during the floral transition, which in annual plants often is closely linked to senescence processes. These authors identified the blue-light photoreceptor CRYPTOCHROME 2 (CRY2) as a trigger for the development-dependent restructuring of chromatin, suggesting an involvement of the light-signalling pathway towards large-scale chromatin modulation. Like floral transition, senescence is a major developmental step accompanied by substantial alterations in gene expression (Breeze *et al.*, 2011). Several authors have shown that global chromatin structure also changes in the nuclei of senescing cells in both the animal and plant kingdom (Drumm and Nagl, 1982; Kolodziejek *et al.*, 2007; Damri *et al.*, 2009; Ay *et al.*, 2009; De Cecco *et al.*, 2013). In *Arabidopsis* plants, Ay *et al.* (2009) analysed alterations in the distribution of euchromatic and heterochromatic histone modification marks in interphase nuclei of mesophyll cells, showing that clear heterochromatic clusters disintegrate at the onset of senescence. Interestingly, by using plants overexpressing the *SUPPRESSOR of VARIEGATION HOMOLOG 2* (*SUVH2*), which was reported to lead to ectopic formation of heterochromatin (Naumann *et al.*, 2005), senescence-dependent heterochromatin decondensation was strongly blocked, even at advanced senescence stages (Ay *et al.*, 2009). So far, it remains unclear if the observed decondensation of large chromatin regions at centromeric and pericentric regions starting at the early stages of leaf senescence is simply an accompanying consequence of nuclei disintegration or is an intended process enabling this important developmental switch. To resolve this question, generating senescence-inducible gain-of-function and loss-of-function plants of known key players for heterochromatin organization like the abovementioned SUVH2 (Naumann *et al.*, 2005) or others like METHYLTRANSFERASE 1 (MET1) (Tariq *et al.*, 2003) or VARIANT IN METHYLATION 1 (VIM1) would be a very useful tool and could improve our understanding of the early starting chromocentre disintegration.

There are a few reports that describe global chromatin alterations induced by stress conditions. Santos *et al.* (2010) analysed changes in heterochromatic domains (45S, 5S rRNA gene loci and centromeres) in root interphase nuclei, which were caused by saline and heat stress. Another study performed by Pecinka *et al.* (2010) demonstrated that, after long-term heat stress, about 50% of the nuclei in stressed leaves were characterized by massive chromocentre dissociation. Interestingly, this decondensation was not observed in nuclei

Table 1. *Techniques used for investigation of epigenetic mechanisms*

Technique	Description	References
Immunocytochemistry	Method to study spatial distribution patterns of DNA-binding proteins and histone modifications by antibody staining. A specific primary antibody binds to its target and a secondary antibody, coupled with the fluorophore, recognizes the first antibody. The distribution of the target is visualized by fluorescence microscopy.	Sauer *et al.* (2006); Nic-Can *et al.* (2013); Pandey *et al.* (2013)
Fluorescence *in situ* hybridization	Technique to localize certain DNA sequences by specific DNA probes, which are coupled with a fluorochrome. The target position is visualized by fluorescence microscopy.	Trask (1991); Fransz *et al.* (1998)
Chromatin immunoprecipitation (ChIP)	Analysis of DNA–protein interactions and occurrence of histone modifications. After chromatin fragmentation, antibodies, e.g. against a specific histone modification or DNA-binding protein, are used to precipitate protein–DNA complexes. Isolated DNA fragments can be identified by PCR or qRT-PCR.	Gendrel *et al.* (2002); Haring *et al.* (2007); Saleh *et al.* (2008)
ChIP-on-chip, ChIP-sequencing (ChIP-seq)	ChIP technique combined with microarray or next-generation sequencing (NGS) for genome-wide analysis of DNA methylation, histone modifications, and binding sites of transcription factors and other DNA-binding proteins.	Huebert *et al.* (2006); Park (2009); Kaufmann *et al.* (2010)
Methylated DNA immunoprecipitation	Technique for examination of DNA methylation patterns on a local or global scale with specific antibodies recognizing methylated DNA. Identification of precipitated DNA fragments by PCR, NGS, or microarray.	Jacinto *et al.* (2008); Laird (2010)
Bisulfite sequencing	Method to investigate DNA methylation patterns of selected genomic regions by bisulfite treatment at single-base resolution. Thereby, only unmethylated cytosines are converted to uracil, whereas 5-methylcytosines are unaffected. After sequencing, unmethylated cytosines are detected as thymines.	Lister *et al.* (2008); Laird (2010); Foerster and Mittelsten Scheid (2010)
Whole-genome bisulfite sequencing	This technique couples bisulfite treatment with NGS, allowing analysis of methylation status of each cytosine in the genome.	Laird (2010)

from meristematic tissues. Taken together, these findings indicate that the three-dimensional organization of chromatin undergoes a similar alteration of heterochromatic patterns in the nuclei during different developmental stages like flowering or senescence and also in response to stress.

Epigenetic mechanisms affecting senescence and linked pathways

The switch from a mature leaf to a senescent leaf depends on internal and external signals and is linked to other developmental processes, such as flowering, and also to the changing abiotic and biotic environment of the plant. Recent findings have shown that such major developmental switches, as well as major responses to the environment, are controlled by higher-order epigenetic mechanisms, which affect the chromatin structure at specific loci and thereby regulate expression of associated genes. In a narrow definition, epigenetic changes are heritable. In this review, we use a broader concept of 'epigenetics' as a mechanism regulating gene expression via changes in chromatin structure, which can be inherited or not. Such epigenetic control is exerted via different mechanisms comprising changes in DNA methylation (Gehring and Henikoff, 2007; Zilberman and Henikoff, 2007), the action of non-coding RNAs (ncRNAs) (Zhou *et al.*, 2010), covalent histone modifications (Kouzarides, 2007; Pfluger and Wagner, 2007), and ATP-dependent chromatin remodelling (de la Serna *et al.*, 2006; Jerzmanowski, 2007), including deposition of histone variants (March-Diaz *et al.*, 2008; Zlatanova and Thakar, 2008; Wollmann *et al.*, 2012). The different ways of epigenetic control, which require a plethora of regulatory factors, are often interdependent and interact with each other in a complex network (Tariq and Paszkowski, 2004; Henderson and Jacobsen, 2007; Saze *et al.*, 2012). In the following chapters, we review several epigenetic mechanisms known to affect chromatin structures in relation to plant development, especially senescence, and senescence-related pathways of abiotic and biotic stress responses. In this review, we will not include the rapidly rising literature on the actions of ncRNAs, which are summarized in several recent publications (e.g. Spiegelman *et al.*, 2013; Ding *et al.* 2013; Wu, 2013).

Control via DNA methylation

The overall status of DNA methylation is controlled by both DNA methyltransferases and DNA demethylation enzymes. DNA, for the most part, can be methylated at cytosine nucleotides yielding 5-methylcytosine. In plants, cytosine methylation appears symmetrically (CG and CHG where H is adenine, cytosine, or thymine) and asymmetrically (CHH) (Vanyushin and Ashapkin, 2011). Correspondingly, three functional classes of DNA methyltransferases exist, which are involved in *de novo* formation and maintaining the methylation at CG, CHG, or CHH sites. DOMAINS REARRANGED METHYLTRANSFERASE 2 (DRM2) catalyses the *de novo* methylation of both symmetric and asymmetric sites. ncRNAs, which guide the silencing complexes that repress genes post-transcriptionally and/or transcriptionally in a sequence-specific manner, are involved in this process (reviewed by Law and Jacobsen, 2010). DRM2 is also responsible for maintenance of the methylation at CHH sites. Methylation at CG sites in *Arabidopsis* is maintained by MET1 (Law and Jacobsen, 2010), while maintenance of CHG methylation is realized via CHROMOMETHYLASE 3 (CMT3) activity (Law and Jacobsen, 2010; Feng *et al.*, 2010). Recent results reported by Stroud *et al.* (2013) showed that the different pathways of site-specific DNA methylation interact with each other. Cytosine methylation is reversible and can be removed actively by DNA glycosylases, such as DEMETER (DME) or REPRESSOR OF SILENCING 1 (ROS1) (Choi *et al.*, 2002; Gehring *et al.*, 2006; Agius *et al.*, 2006). In plants, dynamic DNA methylation is believed to target two main functions: firstly, regulation of gene expression by methylation and demethylation at gene promoter and/or body sites, and secondly, protection of genome stability by silencing of repeat sequences, such as transposable elements (TEs) (Chan *et al.*, 2005). Techniques used to study DNA methylation are methylated DNA immunoprecipitation, bisulfite sequencing, and whole-genome bisulfite sequencing (Table 1).

The impact of DNA methylation on plant development was first shown by Finnegan *et al.* (1996) and Cao *et al.* (2003). These authors found that mutations in *MET1*, *DRM2*, and *CMT3* caused genome-wide hypomethylation and pleiotropic developmental defects. Studies using antisense *MET1 Arabidopsis* or tobacco plants showed a number of striking developmental phenotypes, including reduced apical dominance, alterations in flowering time, and curled leaves (Finnegan *et al.*, 1996; Nakano *et al.*, 2000). Kankel *et al.* (2003) further supported these results by *MET1* missense mutations (*met1-1* and *met1-2*). These mutant plants showed delayed flowering and loss of gene silencing. Moritoh *et al.* (2012) recently reported that rice plants lacking OsDRM2 exhibit pleiotropic developmental phenotypes in both vegetative and reproductive stages.

So far, only a few reports examining DNA methylation patterns during senescence exist. Some reports in angiosperm plants have revealed changes in the extent of DNA methylation during ageing and maturation processes (Diaz-Sala *et al.*, 1995; Lambé *et al.*, 1997; Fraga *et al.*, 2002). Nevertheless, there are initial results showing that TEs are released during senescence in *Arabidopsis* (Guo and Gan, 2012) and barley (Ay *et al.*, 2008). TEs constitute a significant portion of plant genomes, especially in crop plants (Feschotte *et al.*, 2002). Due to their mutagenic potential, plants have evolved various ways of epigenetic regulation to prevent transposition of TEs. DNA methylation is one mechanism that impedes transposition. In plants, ncRNAs are responsible for RNA-directed DNA methylation, which suppresses transposon activities (Ito, 2012). Expression of genes playing a role in regulation of DNA methylation could give the first hints to resolve the question of whether senescence and/or the release of TEs is accompanied by an alteration in their methylation pattern. Therefore, using published large-scale expression data by Breeze *et al.* (2011), we checked the transcription pattern during senescence of more than 70 genes, which are either known or suggested to be involved in *Arabidopsis* DNA

methylation processes (Stroud *et al.*, 2013). Interestingly, most of the investigated factors show no altered expression (see Supplementary Table S1 available at *JXB* online). However, 16 genes were significantly regulated at the transcription level in *Arabidopsis*. Fig. 1A shows examples of the expression patterns of *AGO10*, *FVE*, *MET1*, *SDE*, *ROS1*, and *VIM10*. For a better proportionality, we also plotted expression of the known SAG *ANAC083* and the SDG *RPS17* in Fig. 1B. While *MET1*, *ROS1*, and *VIM1* transcript levels strongly decreased before the leaves were fully expanded, *SDE* and *AGO10* transcription levels declined at pronounced senescence stages. Most of the regulated genes were downregulated at different stages of leaf ageing. *FVE* (Fig. 1, Supplementary Table S1) and *FPA* (Supplementary Table S1) were infrequent exclusions and were significantly upregulated during senescence. Taken together with the above-mentioned observation that global heterochromatin alterations occur during leaf senescence, one could imagine that mechanisms keeping retrotransposons under control, by targeting of their transcripts by ncRNAs and heterochromatization, are progressively subverted when cells reach a senescent state, thus allowing transcription and transposition.

It is also known that some TEs become activated, and that DNA methylation patterns alter during stresses like pathogen attack or heat stress (Grandbastien, 1998; Beguiristain *et al.*, 2001; Pecinka *et al.*, 2010). Thus, Bilichak *et al.* (2012) screened the methylation patterns of salt-stressed plants, showing a clear link between salt stress-dependent regulation of gene expression and DNA methylation patterns. Dowen *et al.* (2012) recently reported that pathogen attacks result in dynamic changes in DNA methylation, which in turn lead to the transcriptional activation of defence-related genes. Moreover, they could show that the dynamic DNA methylation alterations within repetitive sequences or transposons occurred in response to the phytohormone salicylic acid (SA), which was accompanied by upregulation of ncRNAs. This response was often coupled with altered transcription of the transposon and/or the proximal gene, suggesting that some of these 21 nt ncRNAs target defence response genes. McCue *et al.* (2012) presented exciting results showing that hypomethylation of the *Arabidopsis Athila* long-terminal-repeat retrotransposon family leads to the production of 21 to 22 nt ncRNAs. These small RNAs in turn regulate the *UBP1b* gene, encoding the RNA-binding OLIGOURIDYLATE BINDING PROTEIN 1B involved in stress response, by targeting the 3′ untranslated region of its mRNA. Furthermore, Tsuchiya and Eulgem (2013*b*) presented recent data for a remarkable mechanism involving the impact of a TE in controlling expression of the *Arabidopsis* disease resistance gene *RECOGNITION OF PERONOSPORA PARASITICA 7* (*RPP7*). This mechanism is based on insertion of the *COPIA-R7* retrotransposon into the first intron of *RPP7*. The authors were able to show that the methylation status of this TE determines the choice between two different *RPP7*-derived transcript isoforms. Thereby, *COPIA-R7* recruits high levels of the repressive histone H3 lysine 9 dimethylation (H3K9me2) modification to intron 1 of *RPP7*, which suppresses the use of a promoter-proximal polyadenylation site. The authors could further prove that the plant homeodomain finger protein ENHANCED DOWNY MILDEW 2 (EDM2), which was shown to control dimethylation of H3K9 and CHG methylation and thus the silencing states of the *Arabidopsis* TEs *Mu1* and *COPIA4* (Tsuchiya and Eulgem, 2013*a*), also affects H3K9me2 levels at *COPIA-R7*. These results suggest that activation of TEs during senescence and senescence-triggering stresses could affect the expression of neighbouring genes, which should be investigated in future in more detail. However, Pecinka *et al.* (2010) showed for *Arabidopsis* that the activation of TEs during prolonged heat stress was almost independent of DNA demethylation but was accompanied by loss of nucleosomes and heterochromatin decondensation. Thus, further studies are needed to clarify the roles of TEs in plant senescence and responses to different stresses. Methylome analyses are needed to find out whether expression alterations of genes and TEs are associated with DNA methylation states or not.

Control via differential histone modifications

Histones can be covalently modified at the post-translational level in many different ways. Mostly, enzymes modify amino acids at the N-terminal protruding ends of the histones, for example via methylation, acetylation, ubiquitination, phosphorylation, or sumoylation (Jenuwein and Allis, 2001; Turner, 2002; Klose *et al.*, 2006). Moreover, amino acids can be methylated once, twice, or even three times. Depending on the type of modification and the modified amino acid at the different histones, transcriptionally active or inactive chromatin states are established. For example, lysine acetylation is correlated with transcriptional activation (Kouzarides, 2007). Whether methylation marks active or inactive chromatin depends on the methylated residue and the number of added methyl groups (reviewed by Liu *et al.*, 2010). All these different modifications which can be analysed by chromatin immunoprecipitation (ChIP; Table 1), act like a histone code which gives the plants an extensive repertoire to alter chromatin state and thus gene expression (Jenuwein and Allis, 2001; Berger, 2007). Dynamic changes in these histone modification marks require the action of histone-modifying enzymes. Many of these enzymes are known, including histone acetyltransferases, histone deacetylases (HDAs), histone methyltransferases (HMTs), and histone demethylases (Pandey *et al.*, 2002; Thorstensen *et al.*, 2011; Lauria and Rossi, 2011). However, the exact functions of the different enzymes are mostly not fully understood. In the following sections, we will first discuss recent findings on the role of differential histone acetylation events controlling senescence processes and also major developmental steps such as flowering and stress responses linked to senescence. We will then focus on histone methylation events related to these processes.

Histone acetylation

One way to unravel epigenetic mechanisms underlying regulatory networks coordinating developmental and stress-responsive processes is to investigate gain-of-function and loss-of-function mutants of known histone-modifying enzymes. In this way, several groups analysed the functions of

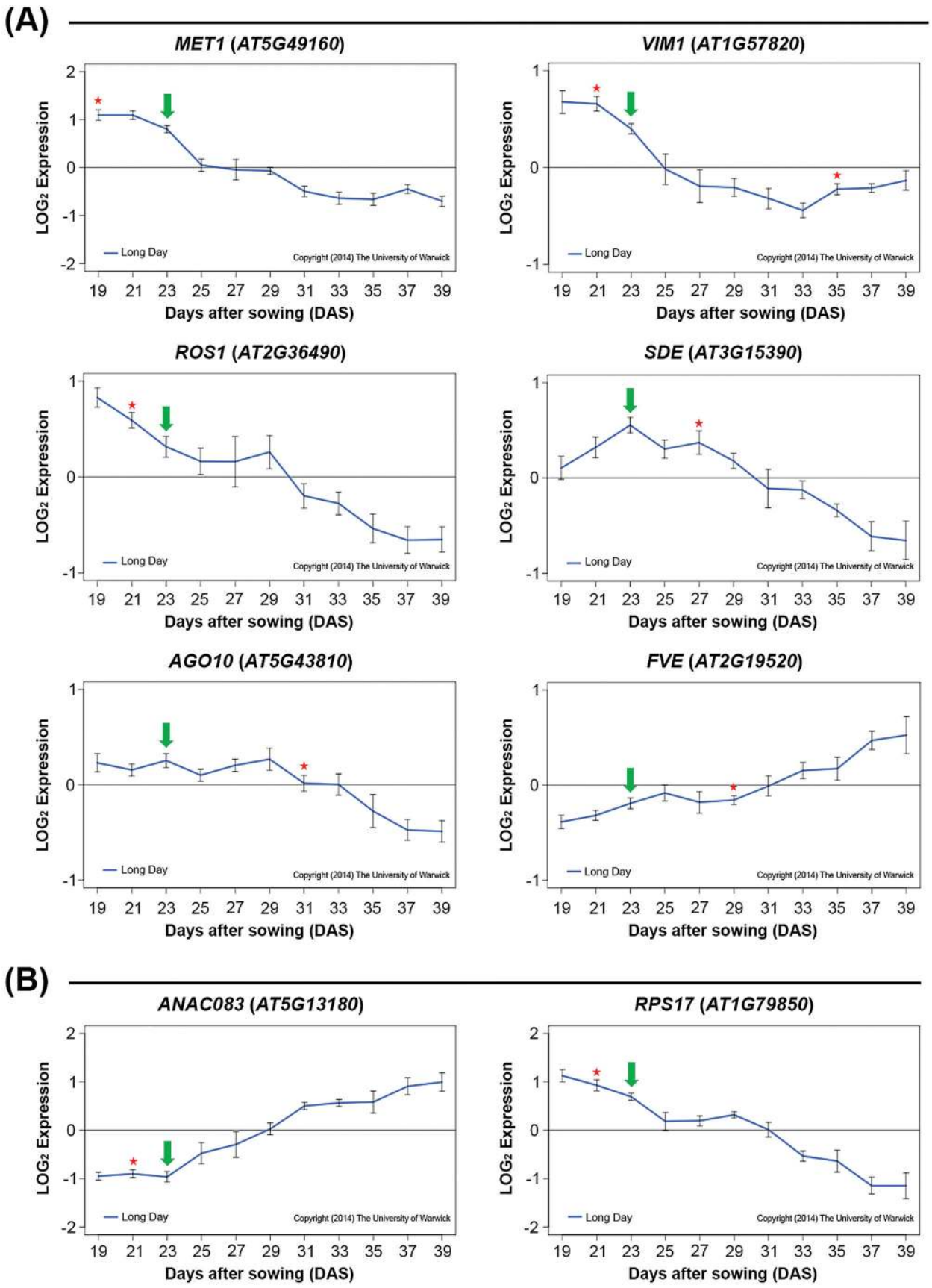

Fig. 1. Expression patterns of genes associated with DNA methylation during leaf senescence. (A) Expression profiles of six of the 16 significantly regulated genes that are associated with DNA methylation. (B) Expression profiles of two senescence marker genes (*ANAC083* and *RPS17*). Expression data published by Breeze *et al.* (2011) were used. The first significant alterations are indicated with red asterisks. Green arrows show the time point at which the rosette leaf #7 that was used was fully expanded. (This figure is available in colour at *JXB* online.)

HDAs. Knockdown mutants of *HDA19* (also called *AtHD1*), which encodes an RPD3-type histone deacetylase, exhibited a pleiotropic developmental phenotype including early senescence, serration, aerial rosette formation, and delayed abnormal flowering (Wu *et al.*, 2000; Tian and Chen, 2001; Tian *et al.*, 2005; Zhou *et al.*, 2005). Transcriptomic analyses of this *hda19* mutant line showed that genes were affected that played a role in plant development processes including senescence and also in stress responses. This fits with many recent publications proving that regulatory pathways of major developmental steps like flowering and senescence and of various biotic and abiotic stress responses are closely linked, forming a coordinated and interrelated network controlling environment-sensitive plant development. Currently, we are far from understanding the molecular basis of this complex regulatory network in detail, but an increasing number of publications, such as those cited above, indicate that epigenetic control mechanisms are involved in this regulatory network forming a higher-order control level. Below, we will summarize recent publications that show in detail that histone acetylation, and later on also histone methylation, is involved in parts of the complex development and stress-response regulatory network.

Choi *et al.* (2012), for example, presented data showing that HDA19 represses SA-mediated defence responses in *Arabidopsis*. Loss of HDA19 activity increased SA content and the expression of a group of genes required for accumulation of SA, as well as pathogenesis-related (PR) genes, resulting in enhanced resistance to *Pseudomonas syringae*. Furthermore, the authors proved a direct association of HDA19 with the promoters of the SA-induced PR genes *PR1* and *PR2*. Consequently, the authors suggested that HDA19 could prevent unnecessary accumulation of SA and that it represses the expression of genes required for SA accumulation under unchallenged conditions. Additionally, Kim KC *et al.* (2008) reported an impact of HDA19 in defence against *P. syringae* through interaction with WRKY38 and WRKY62, two TFs that repress the SA pathway. Interestingly, Zhou *et al.* (2005) showed that *HDA19* is induced by the necrotrophic plant pathogen *Alternaria brassicicola* and application of jasmonic acid. They also demonstrated that overexpression of this gene enhances fungal resistance through the activation of ETHYLENE RESPONSE FACTOR 1 (ERF1), an upstream regulator of both jasmonic acid and ethylene pathogen-response pathways, which is also involved in senescence signalling (Sakuma *et al.*, 2002; Nakano *et al.*, 2006; Koyama *et al.*, 2013). Mutants of another RPD3-type histone deacetylase, HDA6, also show pleiotropic effects on development and stress responses, for example in pathogen responses, senescence, and flowering (Wu *et al.*, 2008). Loss of function of HDA6 also affects the expression of senescence-associated genes like *SAG12* and *SEN4*. Another aspect of this central epigenetic regulatory factor is its effect on the flowering gene *FLOWERING LOCUS C* (*FLC*). HDA6 was shown to cause deacetylation of histones associated with this gene, in this way deactivating the expression of the floral repressor (Wu *et al.*, 2008). Taken together, these reports imply a general function of HDA6 and HDA19 in developmental, phytohormone, and stress-regulated histone deacetylation, acting as regulatory nodes in stress and developmental pathways in plants.

In addition to HDA6 and HDA19, other enzymes modifying histones by adding or removing acetyl residues play a role in various developmental and abiotic stress responses. One example is the *Arabidopsis* histone acetyltransferase protein GENERAL CONTROL NON-REPRESSIBLE 5 (GCN5), which is associated with the response to environmental cues such as light and cold (Stockinger *et al.*, 2001; Benhamed *et al.*, 2006). There are several reports that the stress- and senescence-associated phytohormone abscisic acid (ABA) triggers signalling, which involves alterations in acetylation levels at histones, associated with stress-responsive genes [e.g. *ABA INSENSITIVE 1* and *2* (*ABI 1* and *ABI 2*), 3-KETOACYL-COA-THIOLASE 1 and 2 (*KAT1* and *KAT 2*), and *RESPONSIVE TO DESSICATION 29B* (*RD29B*)] (Chen *et al.*, 2010; Chen and Wu, 2010). Besides the mentioned HDAs, four HD2 proteins (HD2A, HD2B, HD2C, and HD2D), which are also involved in histone deacetylation, have been identified in *Arabidopsis* (Wu *et al.*, 2000; Dangl *et al.*, 2001; Zhou *et al.*, 2004). Luo *et al.* (2012*a*, *b*) demonstrated the interaction of HD2A, -C and, -D proteins with HDA6 and HDA19 and proposed that these proteins function in the same protein complex. Interestingly, Kuang *et al.* (2011) suggest that HD2-like proteins in longan may interact with ethylene response factors (ERFs) that also regulates gene expression during fruit senescence. ERFs are a large transcriptions factor protein class with a highly conserved AP2/ERF DNA-binding domain, which in turn is widely reported to be involved in regulation of senescence and stress responses (Sakuma *et al.*, 2002; Nakano *et al.*, 2006; Koyama *et al.*, 2013).

Histone methylation

Besides acetylation, methylation of amino acids at the N-terminal ends of histones is a major epigenetic control mechanism of gene regulation. Using ChIP analyses (see Table 1) and subsequent quantification by real time-PCR, Ay *et al.* (2009) showed that in *Arabidopsis* histones associated most notably with 5′ ends of *WRKY53*, encoding a TF playing a central role in senescence regulation (Hinderhofer and Zentgraf, 2001; Miao *et al.*, 2004), are modified in a senescence-specific way. At the onset of senescence, active marks like H3K4me3 are established at *WRKY53*-associated histones, correlating with senescence-induced gene expression of this TF. Differential histone methylation requires the action of HMTs and histone demethylases. Several classes of HMT are known. Overexpression of SUVH2 belonging to the SU(VAR)3–9 (KMTase1) type of HMTs results in an increase in heterochromatic methylation marks at H3K9, H3K27, and H4K20, and in this way causes ectopic heterochromatization (Naumann *et al.*, 2005). In addition to other developmental abnormalities, such as curled leaves, leaf senescence is delayed in these plants (Ay *et al.*, 2009). Using ChIP analyses, the authors showed that, in plants overexpressing *SUVH2*, di- and trimethylation at H3K27 is established in mature and senescent leaves at histones associated with the *WRKY53* locus. This repressive chromatin

indexing correlates with a failed induction of *WRKY53* during senescence in the *SUVH2* overexpression line. Ay *et al.* (2009) also showed that senescence-specific induction of some other SAGs (e.g. *SIRK*, *SAG101*, and *SAG24*) failed to appear in the *SUVH2* overexpression line. *SUVH2* is involved in RNA-directed DNA methylation and is related to transcriptional gene silencing (Kuhlmann and Mette, 2009). Interestingly, in a transcriptome analysis of regulatory genes, Ay *et al.* (2014) showed that overexpression of *SUVH2* altered the senescence-associated induction of a subset of senescence-related regulatory genes, in particular members of the senescence- and stress-associated TF families C2H2s, AP2–EREBPs, WRKYs, and NACs. Moreover, targets of the ELONGATED HYPOCOTYL5 (HY5) bZIP TF and genes encoding TFs with an ERF-associated amphiphilic EAR motif were affected preferentially by *SUVH2* overexpression. EAR motif-containing repressors are suggested to play an important role in coordinating environmental and developmental responses via the recruitment of co-repressors such as SAP18 and TPL or related proteins, which in turn facilitate HDA-mediated chromatin modification at target genes (reviewed by Kagale and Rozwadowski, 2011). This implies that at least a part of the regulatory network of senescence is under the control of epigenetic mechanisms. Besides *SUVH2*, nine *SUVH* genes and five *SUVR* genes encode proteins in *Arabidopsis* similar to the *Drosophila* histone H3K9 methyltransferase SU(VAR)3–9. The transcription levels of two of these genes (*SUVH4* and *SUVR4*; Supplementary Table S1) are significantly decreased, suggesting a role for these genes during leaf senescence. Future experiments will elucidate whether the downregulation of these genes has relevance for senescence processes or is a consequence after completion of the growth stages of leaf development. Recently, ChIP-sequencing (ChIP-seq) analyses were performed comparing green leaf material with senescing leaves to observe genome-wide changes in the marks H3K4me3 and H3K27me3, linked to either active or repressive chromatin, respectively (Brusslan *et al.*, 2012). These global analyses indeed showed that at a subset of SAGs the euchromatic mark H3K4me3 was established at onset of senescence, while it was removed from genes that were downregulated during senescence.

Mutations in CURLY LEAF (CLF), a HMT, which is a Polycomb repressive complex 2 subunit, result in early flowering and pleiotropic phenotypes including curled leaves in *Arabidopsis* (Schubert *et al.*, 2006). It could be shown that CLF is required to repress floral homeotic genes such as *AGAMOUS* (*AG*) and *SHOOTMERISTEMLESS* (*STM*). Two HMTs of the SET2 type, SET DOMAIN GROUP 8 and 26 (SDG8 and SDG26), show opposite effects on flowering. While *sdg8* mutants exhibit an early flowering phenotype, in *sdg26* mutants flowering is clearly delayed (Xu *et al.*, 2008). Interestingly, the central repressor of flowering FLC acts in a temperature-dependent manner. Low ambient temperatures in winter result in inhibition of *FLC* (Reyes, 2006). Before this vernalization process, *FLC* is transcribed, preventing the plant from flowering and prolonging vegetative development (Henderson and Jacobsen, 2007). At this stage, the HMT EARLY FLOWERING IN SHORT DAYS (EFS) (Reyes 2006) has been shown to be associated with this gene, establishing the active mark H3K4me3. After cold-exposure, H3K4me3 disappears, and repressive marks (H3K9me2 and H3K27me3) emerge. Consequently, expression of the repressor FLC is inhibited and the flowering pathway is induced (Bastow *et al.*, 2004; Sung and Amasino, 2004; Finnegan and Dennis, 2007).

Evidence is emerging that both plant defence and leaf senescence are regulated by changes in chromatin structure (reviewed by Alvarez *et al.*, 2010; Humbeck, 2013). Thus, control of key factors involved in these two processes via epigenetic mechanisms could be a tool for crosstalk and fine-tuning of the different gene responses. For example, Alvarez-Venegas *et al.* (2007) showed that the HMT ARABIDOPSIS HOMOLOG OF TRITHORAX1 (ATX1) establishes H3K4me3 patterns and regulates both basal and induced expression of *WRKY70*, encoding a TF suggested to be a molecular integrator of SA and jasmonic acid responses and also to be involved in leaf senescence (Li *et al.*, 2006; Knoth *et al.*, 2007). Besides WRKY70, WRKY6 and WRKY53 are also known to be involved in the regulation of senescence and pathogenesis-related processes (Kalde *et al.*, 2003; Miao *et al.*, 2004; Wang *et al.*, 2009; Besseau *et al.*, 2012; Hu *et al.*, 2012; Moreau *et al.*, 2012). Jaskiewicz *et al.* (2011) demonstrated that priming of regulatory genes like *WRKY6*, *-29*, and *-53* with a synthetic SA analogue results in an amplified response to stress. Interestingly, the priming of these three TFs is associated with an increase in H3K4me3 at their promoters. In summary, these results reinforce the strong relationship of pathogen responses with parts of the senescence processes and suggest that central convergence nodes of senescence and stress responses to pathogens are under the control of similar epigenetic mechanisms. The same applies to abiotic stress responses. Expression of the *SUVH2*, *SUVH5*, and *SUVH6* genes encoding HMTs, for example, decreases in the progeny of salt-stressed plants, suggesting a role for these genes in plant stress adaptation (Bilichak *et al.*, 2012). In addition, expression of drought stress-response genes is also controlled via differential methylation patterns at corresponding genes. Thus, Kim JM *et al.* (2008) reported an enrichment of active H3K4me3 and H3K9ac marks at histones associated with the coding regions of several *Arabidopsis* drought stress-responsive genes (*RD*29A, *RD*29B, *RD*20, and *RAP*2.4) during dehydration stress using ChIP. *RD20* and *RAP2.4* are also significantly upregulated during leaf senescence (Breeze *et al.* 2011). Furthermore, Kim JM *et al.* (2008) showed that the stimulation of expression of these genes in response to dehydration correlated with an indexing with activating histone modification marks. In contrast, during rewatering of the plants, these active marks gradually decreased again (Kim JM *et al.*, 2012). Furthermore, Chen *et al.* (2010) showed that gene expression induced by ABA is associated with labelling with activating marks, such as H3K9/14ac and H3K4me3, and a reduction in repressive marks, such as H3K9me2, at histones associated with ABA and abiotic stress-responsive genes (Kim JM *et al.*, 2008). Moreover, by using genome-wide deep-sequencing (ChIP-seq) analysis, van Dijk *et al.*

(2010) unravelled the global epigenomic map of H3K4me1, H3K4me2, and H3K4me3 abundance during drought stress in *Arabidopsis*. Using this approach, they determined substantial alterations in histone modification patterns, mostly in H3K4me3. In addition, Zong *et al.* (2013) demonstrated, via genome-wide analyses, drought stress-responsive changes of H3K4me3 at several stress-induced genes in rice.

Control via ATP-dependent chromatin remodelling factors

In addition to the above-mentioned post-translational modifications of histones, the incorporation of histone variants (not discussed in this review) and the mobilization of nucleosomes by ATP-dependent chromatin remodelling complexes confer a very flexible structure to the chromatin. Dependent on chromatin and ATP hydrolysis, these remodelling factors influence chromatin structure in general and possess the ability to disrupt or to move, destabilize, eject, or restructure nucleosomes in a non-covalent manner (Fan *et al.*, 2004; Jerzmanowski, 2007). Such remodeller complexes can contain histone-binding motifs, such as bromo- and chromodomains, recognizing covalent histone modifications. Via interaction with these moieties, chromatin remodelling complexes are recruited to specific target sites of chromatin (reviewed by Clapier and Cairns, 2009; Hargreaves and Crabtree, 2011). A large set of proteins, like the SWITCH/SUCROSE NONFERMENTING (SWI/SNF) chromatin remodelling enzymes, is known to be involved in restructuring of the chromatin. Different mutants of SWI/SNF subunit proteins exhibit severe developmental aberrations such as dwarf stature, inhibition of root elongation, leaf curling,

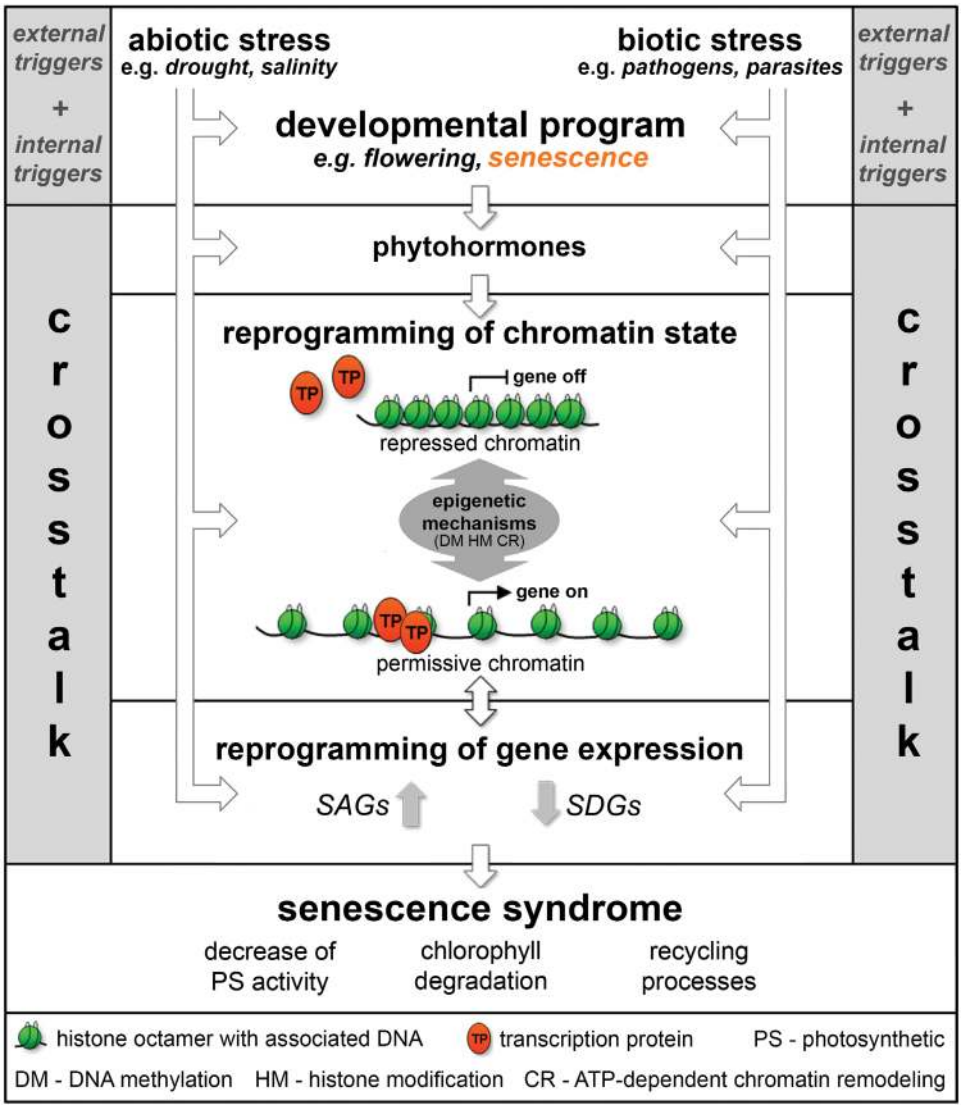

Fig. 2. Model of the regulatory pathway controlling senescence in plants. The leaf senescence programme is influenced by developmental and stress-related triggers, leading to the induction of senescence-associated processes like the recycling of resources, a decrease in photosynthetic (PS) activity, and chlorophyll degradation. Thereby, many genes alter their expression and are either upregulated (SAGs) or downregulated (SDGs). This reprogramming of gene expression is controlled at different levels including the action of TFs but also by higher-order epigenetic mechanisms. Epigenetic control operates via different but interacting processes including DNA methylation (DM), histone modification (HM), and chromatin remodelling (CR). These mechanisms act via dynamic alterations in chromatin status, switching from transcriptionally repressed heterochromatin not accessible to DNA-binding proteins, and permissive, actively transcribed euchromatin allowing the interaction of transcription proteins (TPs).

aberrant stamen development, reduced fertility, alterations in the number and development of flower organs, and complete male and female sterility (Sarnowski *et al.*, 2005).

Another example of a chromatin remodelling protein that regulates developmental processes is the chromatin architecture-controlling AT-hook protein ORESARA 7 (ORE7). Thus, Weigel *et al.* (2000) reported several developmental abnormalities like late flowering or atypical leaf morphology for an activation-tagged mutant line of *ORE7*. Moreover, Lim *et al.* (2007*a*, *b*) showed a strong delay in leaf senescence for overexpressing lines and an activation-tagged mutant of *ORE7*. For the latter, the authors further showed that 368 genes out of 1096 genes differentially expressed in this mutant were associated with senescence processes, suggesting that chromatin remodelling via this AT-hook protein is involved in regulation of leaf senescence. Lim *et al.* (2007*a*, *b*) showed further results suggesting that the senescence-associated protein ORE7 affects chromatin structure. However, besides ORE7, other chromatin-modifying proteins could also be involved in the regulation of senescence-specific gene expression. Published expression data from the global transcriptomic approach by Breeze *et al.* (2011) revealed that some SNF2 family genes such as *CHR10* [*ALTERED SEED GERMINATION 3* (*ASG3*)] and *CHR19* (*ETL1*) are significantly upregulated during senescence (Supplementary Fig. S1 at *JXB* online), suggesting a function of these factors within the senescence processes. Future analysis will elucidate whether the encoded proteins are indeed involved in chromatin remodelling processes during senescence and whether alterations in chromatin structure control the senescence programme directly, or indirectly via other pathways.

Impacts of chromatin remodellers during biotic and abiotic stresses have been comprehensively reviewed by Kim *et al.* (2010). For example, CHR12, a SNF/Brahma (BRM)-type chromatin remodelling factor in *Arabidopsis*, acts as a negative regulator in the growth arrest caused by heat and drought stress (Mlynárová *et al.*, 2007). Recently, the SWI2/SNF2 chromatin remodelling ATPase BRAHMA (BRM) was implicated to play a role in stress response in *Arabidopsis*. Thus, Han *et al.* (2012) ascertained an increased drought tolerance phenotype for *brm* mutant plants. Moreover, they showed that destabilization of nucleosomes occurred if BRM activity was lost.

Concluding remarks

Like all living organisms, plants have to perceive and respond to a full range of biotic and abiotic signals in order to optimize their growth and reproduction. Consequently, due to their almost sessile living style, plant developmental stages like senescence are driven by regulatory pathways that are tightly linked to other developmental and stress response signalling networks (Fig. 2). Senescence involves major reprogramming of gene expression, and recent research has uncovered complex regulatory mechanisms, including the hierarchical action of many TFs, but also a higher-order regulation via alterations in chromatin structure. This review focused on this epigenetic control level downstream of senescence-inducing signals, which is connected to the overall developmental programme and to environmental cues. Evidence is rapidly increasing that gene regulation of these pathways includes differential changes in chromatin status, switching from transcriptionally inactive heterochromatin to actively transcribed euchromatin, and vice versa. This control level is implemented by different but interacting and often interdependent epigenetic mechanisms, including DNA methylation, covalent histone modifications, and non-covalent chromatin remodelling, steering downstream expression of SAGs but also regulating other developmental and stress-related genes.

Recent publications have helped to elucidate some important factors like HDA6 or ORE7 that are involved in the chromatin-dependent changes in gene expression during senescence and senescence-associated processes. Furthermore, an increasing number of reports about dynamic alterations of post-translational modifications at histones has shown a correlation with gene expression during senescence and linked pathways, making us look forward keenly to exciting upcoming findings. Nevertheless, we are still far from understanding the mechanisms behind this control at the chromatin level. Future challenges will be to deepen and complete the analyses of the senescence epigenome, to identify more key players, and to understand the interplay between the different chromatin alterations. Beside the above-mentioned approaches and techniques, proteomic analyses are also needed to gain more insights into the complex interacting epigenome. Moreover, additional layers of complexity, such as the role of ncRNAs or nucleosome deposition during senescence, are under investigation.

Supplementary data

Supplementary data are available at *JXB* online

Supplementary Table S1. Transcription of DNA methylation-associated genes during senescence.

Supplementary Fig. S1. Expression patterns of *CHR10* and *CHR19* during leaf senescence.

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