Epigenetic regulation – contribution to herbicide resistance in weeds?

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Abstract

Continuous use of herbicides has resulted in the evolution of resistance to all major herbicide modes of action worldwide. Besides the well-documented cases of newly acquired resistance through genetic changes, epigenetic regulation may also contribute to herbicide resistance in weeds. Epigenetics involves processes that modify the expression of specific genetic elements without changes in the DNA sequence, and play an important role in re-programming gene expression. Epigenetic modifications can be induced spontaneously, genetically or environmentally. Stress-induced epigenetic changes are normally reverted soon after stress exposure, although in specific cases they can also be carried over multiple generations, thereby having a selective benefit. Here, we provide an overview of the basis of epigenetic regulation in plants and discuss the possible effect of epigenetic changes on herbicide resistance. The understanding of these epigenetic changes would add a new perspective to our knowledge of environmental and management stresses and their effects on the evolution of herbicide resistance in weeds. © 2017 Society of Chemical Industry

Keywords: DNA methylation; epigenetics; gene expression; gene regulation; herbicide detoxification; plant stress response

1 INTRODUCTION

Weed control has become a greater problem in recent decades as a consequence of the evolution of herbicide-resistant weed biotypes. Intense herbicide use favors the evolution of resistance because the herbicides are strong selective agents.1,2 Currently, there are >480 cases (species × site of action) of herbicide resistance reported globally, distributed over 251 species and encompassing resistance to almost all herbicide mechanisms of action.3 Herbicide resistance can be classified into two primary categories: target-site resistance (TSR) and non-target-site resistance (NTSR).2,4 TSR is primarily caused by DNA mutations that change one or more amino acids, thus causing alteration in the enzyme conformation, which prevents herbicide binding at the site of action.5,6 Herbicide resistance caused by mutation of target enzymes is the most frequent process and has occurred for most herbicide mechanisms of action. TSR can also be caused by overexpression of a target enzyme through gene amplification, changes in a gene promoter, or codon deletion.7,8 In contrast, the process of NTSR is more complex and far less understood, with what is known covered in some recent reviews.4,6,10 Some mechanisms include decreased herbicide absorption, translocation and/or enhanced detoxification.11,12

NTSR via enhanced detoxification is considered of particular importance because it can confer unpredictable resistance to multiple mechanisms of action, including compounds never used in the herbicide-resistant weed. Enhanced herbicide detoxification is caused by enzymatic systems detoxifying xenobiotics in plants, mediated primarily by cytochrome P450 monooxygenases (P450s),12 by glutathione transferases (GSTs)13 or by herbicide exclusion attributable to ATP-dependent [ATP-binding cassette (ABC)] transporters.14 However, gene expression and regulation associated with NTSR are poorly understood. It was recently suggested that, in addition to DNA mutations or indels in TSR- or NTSR-related genes, herbicide resistance could also be influenced by epigenetic processes.2,4,15 Epigenetic regulation has been associated with numerous cellular processes such as developmental programming, gene expression, embryonic development, transposon silencing, genome stability and plant stress responses.16–18 Several studies have indicated that the evolution of drug resistance in humans is associated with epigenetic regulation.19,20 Together with genetic variation, epigenetics is one of the factors that contribute to the inter-individual variability in drug response.20 In addition, the variability of expression and function of ABC transporters that mediate drug efflux in cancer cells has recently been explained by epigenetic processes.21 Some cases of resistance to anti-cancer drugs and antibiotic resistance in animals, including resistance conferred by detoxification and
trans-membrane movement of drugs, have similar mechanisms to herbicide resistance in weeds.14,21,22

One of the main questions regarding herbicide resistance is whether sublethal herbicide exposure leads to epigenetic alterations that confer enhanced survival, and if these are transmitted to subsequent generations, leading to eventual resistance development.23 Therefore, the understanding of epigenetic mechanisms and trans-generational processes is important not only for cultivated plants exposed to environmental stresses, but also for weed populations evolving in different field conditions that are exposed to intense herbicide selection pressure. This phenomenon could, in addition to the classical genetic factors, such as gene copy number variation, explain the variability of poorly understood responses of herbicide resistance in some weed species. However, the knowledge of epigenetic processes in weeds is in its infancy and limited to a few possible examples.25 The aims of this paper are to provide basic information about epigenetic processes related to DNA methylation and histone modifications in plants, how they contribute to mitigation of some abiotic stresses and how they can be related to herbicide-resistant weeds.

2 WHAT IS EPIGENETICS?

Epigenetics refers to potentially heritable traits that cannot be explained by modifications in the DNA sequence.24 In a strict sense, epigenetic modulation consists of chemical modification of DNA and/or histone proteins that results in alleles with the same DNA sequence but different patterns of expression (called ‘epialleles’), which are sometimes carried over into subsequent generations.25 Epigenetic mechanisms involve a wide range of biochemical marks, DNA and histone modifications, and various types of non-coding RNAs [e.g. small interfering RNAs (siRNAs)].26 Epigenetic regulation is a dynamic process in which the domains of open, transcriptionally permissive chromatin (the assembly of DNA with histone proteins) can be remodeled into compact structures and transcriptionally repressed or vice versa.17,27

Briefly, epigenetic modifications can be induced spontaneously, genetically or environmentally.28 In many cases, chromatin changes are induced by genetic changes such as gene duplication or transposon insertion (reviewed in Pecinka et al.27). Epigenetic changes are developmentally controlled in every generation, while stress-induced changes are presumably more random and normally revert soon after their occurrence.29 However, it is assumed that, under specific conditions, chromatin changes (DNA methylation, histone modifications and/or exchange of histone variants) may persist for a longer period after stress exposure, providing a ‘stress memory’, and may be inherited across mitotic or even meiotic cell divisions.26 Normally, global erasure of epigenetic changes occurs in germline cells, referred to as epigenetic reprogramming. However, certain genomic regions can escape erasure, allowing the persistence of epigenetic states to be passed to progeny, resulting in transgenerational epigenetic inheritance.30 Thus, in some cases, this response is maintained over many generations and is often captured as natural epigenetic variation (reviewed in Paszkowski and Grossniklaus28).

2.1 DNA methylation in plant genomes

DNA methylation involves the addition of a methyl group to the fifth carbon of cytosine (5-methyl-deoxycytosine (5mC)), and occurs in plants in three functional sequence contexts, CG, CHG and CHH (where H = A, C or T).31 In plants, DNA methylation is established de novo via the RNA-directed DNA methylation pathway guided by siRNAs (reviewed in Matzke and Mosher23) and maintained by three pathways.31,33,34 RNA-directed DNA methylation is responsible for DNA methylation in all sequence contexts, but CHH methylation is a specific hallmark of RNA-directed DNA methylation.17 After establishment, DNA methylation can be perpetuated through both mitotic and meiotic divisions by maintenance DNA methyltransferases.31 DNA Methyltransferase 1 (MET1) maintains CG methylation,33 while Chromomethylase 2 (CMT2) methylates both CHG and CHH contexts31 and Chromomethylase 3 (CMT3) maintains CHG methylation.34

In Arabidopsis thaliana, approximately 6% of all cytosines are methylated in leaf tissues; however, this methylation is not distributed uniformly as 24% of CGs, 7% of CHG and only 2% of CHH sites are methylated.35 In comparison, ~14% of all cytosines in rice (Oryza sativa), which has a much larger genome, are methylated, with c. 52% of CG sites being methylated, 32% of CHG sites and 16% of CHH sites.36 In maize (Zea mays), the average methylation level of all cytosines is close to 20% in leaf blades,37 with 86% of CG sites being methylated, 74% of CHG sites and 5% of CHH sites.38 Hence, the frequency of DNA methylation varies among species and sequence contexts, which reflects the activity of enzymes involved in the establishment, maintenance and removal of methylation.17

Knowledge about the localization of methylation in the genome is important to understand the dynamics of gene expression. Genes with methylated promoters have lower expression levels and they predominantly show tissue-specific expression patterns.18 Two different methylation patterns have been observed in A. thaliana. First, cytosines are methylated in any sequence context in transposable elements, which results in their strong transcriptional silencing. Second, methylation in CG contexts is observed in the exons of approximately 33% of transcribed genes, referred to as gene body methylation, and is correlated with moderate or high transcription.31,35 Gene body methylation has been proposed to play a role in adjusting transcriptional profiles to environmental conditions,30 but its strong reduction in the genomes of Brassicaceae species, such as Conringia planisiliqua and Extrema salisugineum, suggests that it may be largely dispensable in some plants.40

2.2 Histone modifications and variants in plants

The nucleosome is an octamer of two copies each of histones H2A, H2B, H3, and H4, around which is wrapped by 147 bp of DNA, where 14 contact points between histones and DNA are found.41 Histone modifications occur in the N-terminal region, called the histone tail. This region is enriched with lysine (K) and arginine (R), which can be post-translationally modified by methylation, acetylation, phosphorylation and ubiquitination.41,42 The main classes of histone modifiers identified in plants are histone acetyltransferases, histone deacetylases, histone methyltransferases and histone demethylases.42

Histone modifications can alter the permissibility of gene transcription. Generally, the acetylation of lysine residues of histones 3 and 4 (H3 and H4) neutralizes the positive charge of the histone tails, decreasing affinity for DNA as a result of its negative charge. Thus, histone acetylation is often associated with increased gene activity, whereas histone deacetylation is normally correlated with transcriptional repression. The change in the affinity between DNA and histones overcomes the repressive effect of nucleosomes and allows dynamic changes in gene transcription.43 In addition, tri-methylation of the fourth lysine of
H3 (H3K4me3) can activate transcription, while tri-methylation of the 27th lysine of H3 (H3K27me3) installed by Polycomb Repressive Complex 2 (PRC2) represses it. In this way, histone modifications can affect gene expression by acting in chromatin remodeling, and the result of transcription permission or repression will depend on the residue where the modification occurs, the type of modification and its spatial distribution across the gene region.

In addition, entire histone molecules can be replaced by another histone variant, usually loaded after DNA replication, differing in specific amino acids and thus changing the nucleosome properties. For example, the histone variants H2A.Z and HTR12 (CENH3) precisely regulate gene activity and define the functional centromere, respectively. Histone variant H2A.Z replaces H2A in some nucleosomes. H2A.Z-containing nucleosomes are more tightly associated with DNA than nucleosomes with canonical H2A, and the enrichment of this variant is correlated with lower transcription. However, genes with H2A.Z respond to a variety of stimuli (gene responsiveness) and become evicted by higher temperature. While HTR12 is a centromere-specific histone variant that precisely replaces H3 in the centromere region, it makes the centromeric chromatin unique to ensure proper chromosomal segregation in cell division. Although it is accepted that histone modifications and the production of histone variants are important responses under environmental stresses, it is still unknown which is the first step to occur, the changes in transcription patterns or the changes in chromatin, and why some modifications are rapid, while others are gradual and prolonged responses.

2.3 How do epigenetic mechanisms regulate gene expression and mitigate stress in plants?

Epigenetic pathways contribute to survival in unfavorable environmental conditions by triggering defense responses through a network of specific genes. Plant metabolism and cell redox status may play an important role in epigenetic control. Reactive oxygen species (ROS) produced in plant cells during basal processes (respiration and photosynthesis) and stress conditions affect not only metabolic flux, but also chromatin modifications and epigenetic control of gene expression. Plants under stress are often in an energy imbalance that contributes to increased epigenetic changes. This may result in changes in metabolite control of stress-induced chromatin that can involve adenosine triphosphate (ATP), methyl donor S-adenosylmethionine (SAM) and the acetyl donor acetyl coenzyme A (acetyl-CoA). For example, SAM is synthesized from the amino acid methionine, which is the universal methyl donor in methylation reactions that acts as the substrate for histone and DNA methyltransferases. The importance of SAM was demonstrated in a study in rice where genes encoding SAM synthetases were knocked out, resulting in suppression of DNA and H3K4me3 demethylations, and thus late flowering. Therefore, stresses may influence basic plant metabolism and affect the availability of precursors for epigenetic processes, resulting in alterations of expression (activation or silencing) of specific genes.

Chromatin is dynamic and can be altered by developmental or environmental stimuli that impact the accessibility and effectiveness of the transcriptional machinery. Thus, DNA methylation, histone modifications and histone variants altered by environmental stress can affect gene transcription and the transcription rate. For instance, stress conditions can destabilize silencing in DNA methylated regions, enabling the transcriptional activation of specific transposable elements and nearby genes.

For example, heat stress activated ONSEN (a copia-type retrotransposon) conferred heat responsiveness through activation of nearby genes by changing DNA methylation levels using the siRNA pathway in A. thaliana seedlings. Another example is LINE retrotransposon-mediated accumulation of pigments, possibly with protective functions, during cold stress in the pulp of blood oranges. This indicates potentially important, but so far relatively poorly understood, roles of transposable elements in the control of gene transcription under stress.

Plant histone modifications occur in response to a wide range of abiotic stresses, including salt, heat and cold. The enzymes that perform histone acetylation and deacetylation (histone acetyltransferases and histone deacetylases, respectively) have antagonistic activities that are influenced by the pool of acetyl-CoA, because histone acetyltransferases use acetyl-CoA as a substrate to acetylate histone lysine residues. Furthermore, histone acetyltransferases interact with transcription factors and are associated with activating stress-response genes. In addition, environmental conditions and endogenous signals can repress target genes by decreasing histone acetylation levels. For example, Histone Deacetylase 19 (HDAC19) is able to regulate gene expression involved in jasmonic acid and ethylene signaling of the pathogen response in A. thaliana. The expression of different histone deacetylases in rice is also differentially regulated in response to osmotic stress by abscisic acid, gibberellic acid and salicylic acid. These effects together suggest that a ‘metabolic decision’ may epigenetically regulate responses to stresses.

The majority of the stress-induced epigenetic changes only persist for the duration of the stress exposure, after which both chromatin and expression patterns return to their pre-stress state. However, some changes may persist for longer after returning to favorable environmental conditions. Nevertheless, evidence exists for stress-induced heritable chromatin modifications that are carried over for multiple generations, thereby improving fitness.

3 HOW EPIGENETIC PROCESSES CAN BE INVOLVED IN HERBICIDE RESISTANCE

Herbicide resistance is an important example of rapid plant evolution, and is increasing worldwide. The large number of individuals exposed to strong selection pressure greatly contributes to the selection of herbicide-resistant biotypes. High herbicide doses have been suggested to result in high resistance levels by selecting for rare TSR alleles primarily associated with mutations in the gene that codes for the herbicide target enzyme. However, sublethal herbicide doses can also select for resistance, perhaps through the recurrent enrichment of several minor additive genes related to NTSR. Sublethal herbicide doses are commonly experienced by weeds in crop fields as a result of drift, incomplete coverage, over-topping crop canopies, or intentionally applied low rates. Over time, low doses can increase the frequency of plants that have accumulated different alleles, causing a reduction in herbicide sensitivity at the population level, which occurs faster in cross-pollinated species that can rapidly accumulate resistance genes. Repeated cycles of selection by sublethal herbicide doses leads to the eventual appearance of herbicide-resistant biotypes. Sublethal rates of acetyl-coenzyme A carboxylase (ACCase) inhibitor herbicides over generations of Lolium rigidum increased the mean population survival after some cycles of selection. The application of a series of ACCase herbicides increased resistance in L. multiflorum, although the
increase in resistance was not transmitted to offspring, shedding light on the mechanism of the acclimation response.62

Spontaneous mutation rates from 7 x 10-9 to 2.2 x 10-8 base substitutions per site per generation were identified in A. thaliana.63,64 A methylated cytosine is more likely to be mutated under natural conditions than a non-methylated cytosine.65 The analysis of spontaneous variation of DNA methylation in A. thaliana plants originating from single-seed descendent for 30 generations identified 114 287 CG single methylation polymorphisms and 2485 CG differentially methylated regions that differed from the ancestral state, contributing to phenotypic diversity.66 Although this is a relatively high number, it has to be considered that methylation-based silencing usually does not depend on a single (non-)methylated site.67 Therefore, most of the loci containing polymorphic DNA methylation sites remain without obvious effect. Loss or gain of DNA methylation over a larger region with a potential phenotypic change seems to occur at a frequency similar to that for DNA mutations in A. thaliana.68

Plants have evolved the ability to cope with abiotic environmental stresses by re-programming gene expression. One of the mechanisms that modifies transcriptional responses is related to changes in chromatin status, as previously described.18 Many herbicides cause oxidative stress similar to some abiotic stresses in plants.56 Thus, most of the enzymes involved in metabolizing herbicides are involved in the basal stress response pathways in plants, including detoxification of ROS resulting from stress conditions.12,13 However, whether the stress caused by the herbicide could trigger transient or even stable epigenetic changes is not known. This knowledge could modify the way that resistance is defined based on an exclusively ‘inherited’ trait,22 because epigenetic regulation could contribute to transient survival of herbicide stress. Epigenetic mechanisms could help explain rapid adaptation of weeds to herbicide selection pressure through alterations in gene expression or changes in activity of transposable elements that can also affect gene expression or even lead to gene duplication.

A recent study with atrazine in rice indicated that most DNA methyltransferases, histone methyltransferases and DNA demethylases were differentially regulated in response to the herbicide.36 Epigenetic alterations were involved in activation of specific genes responsible for atrazine detoxification. In Triticum aestivum, different glyphosate concentrations increased the levels of global DNA methylation from 28 to 74%.67 Sublethal glyphosate doses induced dose-dependent differentially methylated regions across the A. thaliana genome. Interestingly, >90% of the affected genes are not modified by other abiotic stresses, suggesting that many epigenetic changes may be stress-specific.68 These epigenetic mechanisms could be related to the ‘flipped on’ or ‘flipped off’ control of genes such as P450s, GSTs and ABC transporters or transcription factors important for herbicide detoxification.

Our initial studies with sublethal doses of imazethapyr, glyphosate and 2,4-dichlorophenoxyacetic acid (2,4-D) indicated that herbicide susceptibility was increased in some A. thaliana mutants with changes in specific epigenetic pathways of DNA and histone methylation, especially in mutants for Repressor of Silencing 1 (ROS1) (Markus C, Pecinka A and Merotto Jr A, unpublished). ROS1 is a 5-methylcytosine glycosylase, which is a major DNA demethylase that removes DNA methylation for dynamic transcriptional regulation and can contribute to increased expression of specific genes.69 This suggests that epigenetic pathways may influence the regulation of genes important for herbicide detoxification.

A model for the putative role of epigenetic changes in the evolution of herbicide resistance in weeds is suggested (Figure 1). This model is based on the system proposed to explain the epigenetic regulation caused by other abiotic stresses26 and the overall model of NTSR that indicates how plant cells receive herbicide stress signals via sensors.2 After the application of sublethal herbicide doses, the signaling pathways triggering general and specific responses are activated. Primary and secondary signals involved in metabolite alteration induce changes in specific pathways, as the herbicides may activate existing stress-response pathways.70 The signal is transduced to regulators and triggers the regulation cascade(s). Plants that do not have resistance alleles will suffer cell and plant death (brown leaf in Figure 1). Processes of transcriptional and post-transcriptional control can act on expression and regulation of genes important for herbicide resistance (P450, GST and ABC transporters). The signal induced by the herbicide (regulation cascade) could also trigger metabolite alteration that induces changes in expression and/or activity of RNA-directed DNA methylation, histone variants and histone modification enzymes that induce epigenetic changes. The alteration of epigenetic enzymes and pathways can induce changes in genes involved directly or indirectly in herbicide resistance, which can persist into subsequent generations. Some modifications revert when the plant overcomes the stress, showing that they were transient changes involved in acclimation. Other alterations can be retained mitotically and/or meiotically, providing a ‘stress memory’. If mitotic heritability is present, the ‘stress memory’ will persist during the current generation, and if both mitotic and meiotic heritabilities exist, this will result in transgenerational persistence for one or more generations (Figure 1).

Thus, herbicide resistance, particularly through NTSR, may involve epigenetic mechanisms. Some of these responses may be general stress responses, but others may be herbicide specific. Much remains to be elucidated regarding epigenetics and NTSR, especially considering the large number of herbicide chemistries. Indeed, there are likely to be species-herbicide-specific changes that lead to resistance development. Additionally, the intra-generational stability and transgenerational potential of these epigenetic changes must be studied to identify their potential to confer herbicide resistance over a long period. Rapid local adaptation to herbicide stress may be partly mediated by epigenetic control over gene expression.

4 CONCLUDING REMARKS

The rapid evolution of herbicide resistance and the variety of herbicide resistance mechanisms observed today are a challenge for weed management and herbicide use, especially with the increasing problem of metabolic resistance. Epigenetic mechanisms have been well described as important regulators of plant–environment interactions, mainly associated with stress adaptation. Environmental conditions affect plant physiology, which can cause variation in the expression of herbicide resistance. Additionally, there is increasing evidence that herbicides can trigger epigenetic responses, such as that provided by initial studies in rice, wheat and A. thaliana. In the scenario where sublethal doses of herbicides may act similarly to other abiotic environmental stresses, it is important to consider genetic and environment interactions to predict and properly monitor the evolution of herbicide resistance. Establishment of stable epigenetic effects following herbicide treatment would allow fast development of ‘memory’ of herbicide treatments in complex...
Epigenetic regulation of herbicide resistance

Signal transduction; primary and secondary stress signals: changes in metabolite balance (ROS, etc).

Alterations in epigenetic regulators: small RNAs, RNA-directed DNA methylation components, histone variants, histone modification enzymes.

Possible changes: histone variants, histone modification and DNA methylation.

GENE REGULATION OF HERBICIDE RESISTANCE:
- NTSR related genes: P450s, GSTs, ABC transporters, transcription factors;
- TSR genes related to overexpression of target enzyme;
- Other mechanisms.

Mitotically and meiotically: Very stable stress induced gene regulation (transmitted to progeny), Transgenerational ‘stress memory’.

Heritable changes.

Non-heritable within generation changes, not transmitted to progeny.

Reversible stress-responsive gene regulation.

Short-term stress stable response gene regulation.

Resistance within generation ‘stress memory’, i.e. acclimation.

weed genomes and thus accelerate the evolution of resistance, particularly NTSR. The development of basic molecular knowledge in weeds and the advance of epigenetic studies related to herbicide resistance will open up a new avenue for the understanding of weed adaptation to herbicides.

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