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Transgenerational epigenetic inheritance in plants★

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Abstract

Interest in transgenerational epigenetic inheritance has intensified with the boosting of knowledge on epigenetic mechanisms regulating gene expression during development and in response to internal and external signals such as biotic and abiotic stresses. Starting with an historical background of scantily documented anecdotes and their consequences, we recapitulate the information gathered during the last 60 years on naturally occurring and induced epialleles and paramutations in plants. We present the major players of epigenetic regulation and their importance in controlling stress responses. The effect of diverse stressors on the epigenetic status and its transgenerational inheritance is summarized from a mechanistic viewpoint. The consequences of transgenerational epigenetic inheritance are presented, focusing on the knowledge about its stability, and in relation to genetically fixed mutations, recombination, and genomic rearrangement. We conclude with an outlook on the importance of transgenerational inheritance for adaptation to changing environments and for practical applications. This article is part of a Special Issue entitled “Epigenetic control of cellular and developmental processes in plants”.

Keywords

Plant stress; Heritable stress effects; Epigenetics; Genome stability

1. Introduction

Generations of life scientists have contributed to our current view that selection, acting on randomly generated genetic variations or polymorphisms, is *the* driving force for adaptive responses and organismal evolution. Accordingly, the fact that some genotypes perform better than others under defined environmental conditions, could be seen as being the result of sheer luck.

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This dogma of genetic inheritance and evolution has been challenged repeatedly by Lamarckian viewpoints, which also occurred for ideological reasons in the Soviet Union and countries of the former Eastern Block [1–4]. One could start with the enigmatic character Paul Kammerer, an Austrian biologist trying to make a strong case for Lamarckism at the beginning of the 20th century. This involved experiments on regenerative capacities of *Ciona* (a tunicate) as well as his infamous attempts to prove heritable environmental effects on the anatomy of midwife toads (*Alytes obstetricans*) [5]. Given that some of these experiments appear to have been fabricated, which might have contributed to Kammerer's decision to put an end to his life, it is astounding to note that his legacy still causes some dispute in the scientific community [5–9]. Somewhat more far-reaching consequences arose from the doctrines represented by the agronomist Trofim Lysenko and his followers. Based on experiments addressing vernalization in wheat, he came up with a concept aiming to substantially improve crop qualities via inheritance of acquired phenotypic traits [10]. The resulting denial of Mendelian genetics also ruined the careers of numerous brilliant scientists in the Soviet Union, which makes it perhaps understandable that any attempt to rehabilitate such Lamarckian positions is considered, at the very least, problematic [11]. Even today, when viewing arguments of proponents of 'Intelligent Design' we are confronted with attempts to challenge well-established evolutionary concepts without offering any scientifically valid support for such divergent hypotheses [12,13]. Thus, when it comes to transgenerational inheritance of acquired characteristics, a skeptical viewpoint appears justified.

1.1. Transgenerational epigenetic inheritance

1.1.1. Historical perspectives—Epigenetic responses are caused by variations in epigenetic marks, that is, reversible enzyme-mediated modifications of DNA or associated histones that control transcriptional activity of genes, repetitive sequences, and transposable elements and thus, are important regulators of genome integrity in higher eukaryotes [14].

Here, it is important to discriminate between inheritance of established epigenetic marks upon formation of specialized cell files in multicellular organisms, and the inheritance of such epigenetic marks across generations. Intraorganismal inheritance of epigenetic marks can be traced back to Conrad Waddington who originally postulated the concept as a means of explaining the fact that diverse cell types that constitute a multicellular organism can arise from only a single genome [15–18]. In contrast, transgenerational epigenetic inheritance requires the passage of epigenetic marks, such as DNA methylation, through the germline without being erased by surveillance mechanisms that ensure establishment of cellular totipotency at the onset of ontogenesis [19,20]. Erasure of epigenetic marks, in early developmental stages, is well documented in mammals, but its relevance for developmental decisions made during plant embryogenesis is less well understood [21]. Nevertheless, the observation that epigenetic alleles (i.e., epialleles) are stably inherited over several generations in a wide range of organisms, including plants indicates that the resetting to an epigenetic 'default-state' is seemingly a leaky process (Table 1).

For a long time, only limited genetic and molecular evidence pointed towards transgenerational epigenetic inheritance mechanisms. Some important early experiments

were undertaken in higher plants, such as those addressing the mechanisms underlying pigment variations in corn lines that could not be explained by conventional Mendelian segregation [22]. These early studies involved analyses of the maize *r1* and *b1* loci that can switch between distinct epiallelic states that, in turn, heritably affect kernel pigmentation [23–25]. This phenomenon, known as paramutation, depends on regulatory crosstalk between distinct alleles in a heterozygous state, causing inherited alterations in the expression status of one of the alleles involved (also called paramutable allele). The switch to a then-paramutagenic allele is stably inherited through meiosis and furthermore, efficiently triggers conversion of naïve paramutable alleles into the paramutagenic state in subsequent generations, which accounts for the non-Mendelian inheritance of such traits [26–28]. With the development of molecular biology tools, some insights into the mechanisms underlying paramutation have become available, and suggest a role for locus-specific DNA repeats and their methylation status, as well as activity of small RNAs, highlighting the epigenetic nature underlying this phenomenon [29–34]. Another well-known plant example for transgenerational epigenetic inheritance relates to a symmetry change in flowers of *Linaria vulgaris* (toadflax) [35]. A change from bilateral to radial symmetry has been associated with increased DNA methylation in the upstream promoter region of the *Lcyc* locus, whereas somatic reversion to bilateral flower symmetry correlates with diminished DNA methylation [36]. Whether or not it is actually inheritance of the observed variation in DNA methylation that causes transmission of the aforementioned altered epigenetic states remains unresolved (Table 1).

Evidence for transgenerational epigenetic inheritance has also been described for non-plant multicellular organisms [37–41]. For example, studies on agouti viable yellow and axin fused epialleles in mice led to the suggestion that variations in chromatin modifications of retrotransposons that insert upstream of the respective loci, drive heritable changes in gene expression [42,43]. However, as with plants, the molecular basis for inheritance of such epigenetic traits is still far from being fully understood [44].

1.1.2. Current implications—A demonstration of transgenerational epigenetic inheritance is consistent with the concept of ‘soft inheritance’, originally coined by Ernst Mayr [45,46]. Unlike the conventional view of a stably inherited genetic material that is subject to mutagenic changes only by chance, soft inheritance suggests an environmental impact on inherited information, thereby allowing for directed transmission of environmental effects into subsequent generations. An example for soft inheritance that has received some attention, specifically in plants, deals with induction of inherited variability of genome organization. Increased genetic variability within a defined gene pool could represent an evolutionary advantage as it might facilitate selection of well-adapted genotypes under adverse environmental conditions [47]. Accordingly, induction and inheritance of increased genetic variability due to reduced genome stability in response to a variable environment could be considered as an adaptation to such altered conditions. Work by Babara Hohn’s group on somatic recombination in *Arabidopsis* supports this view insofar as it was demonstrated that stressful environments triggered an heritable increase in recombination rates [48]. While additional work provided further evidence for a scenario in which environmental signals cause heritable effects on genome and epigenome stability

[49,50] (Table 2), other researchers reported difficulties in reproducing the results originally obtained by the Hohn group [51]. Whether or not induced transgenerational inheritance of environmentally modulated variations on the epigenome will reshape the current views of adaptive evolution remains a matter of debate.

In recent years a number of excellent reviews addressing this controversial topic have been published [41,52–54]. Here we will focus on the interplay between environmental factors and their (heritable) effects on the epigenome in plants. We give a brief introduction of how plants cope with environmental stress and address the molecular switches that contribute to the control of the epigenome and discuss their potential role in transgenerational epigenetic inheritance.

2. Controlling the epigenetic status in plants

Organisms are required to adjust to environmental fluctuations, and selective forces appear to act on environmentally induced modifications in development, a process suggested to be essential for adaptive speciation [55,56]. Epigenetic marks such as DNA methylation, histone modifications, and the generation of regulatory small non-coding RNA molecules, represent an efficient means to modulate gene activity in response to internal and external stimuli [57,58]. The highly dynamic nature of epigenetic adjustments suggests their involvement in heritable adaptive responses via transmission of epigenetic marks from one generation to the next, independently of DNA sequence changes [41,59–64]. An altered epigenetic status can be stably inherited but alternatively, might also exhibit metastable characteristics and will revert after a variable number of replication rounds. The analysis of epigenetic responses is complicated further by its highly variable effects on only a few cells or tissue sectors, whereas in other instances entire individuals can be affected. Yet, once acquired, epigenetic adjustments can be highly stable even on an evolutionary scale [65–67].

At present we have only limited insights into the mechanisms by which epigenetic signals might exert a sustainable impact on quantitative traits in progeny generations. Nevertheless, we have accumulated extensive knowledge on the mechanisms and molecular machinery that could be involved.

2.1. DNA methylation

DNA methylation in eukaryotes denotes addition of a methyl group at position 5 of the pyrimidine ring of cytosine. In plant genomes, cytosine methylation occurs in CG, CHG and CHH contexts (where H is A, C or T), whereas, for example, in somatic cells of vertebrates, cytosine methylation is limited to the CG context [68]. In *Arabidopsis*, CG methylation is maintained by the DNMT1-ortholog MET1 (DNA Methyltransferase 1) and by VIM family proteins (Variation In Methylation), which are orthologs of the mammalian DNMT1-associated factor UHRF1 (ubiquitin-like containing PHD and RING finger domains) [69]. CHG methylation is maintained primarily by the plant-specific DNA methyltransferase CMT3 (Chromomethylase 3), which acts in conjunction with histone methyltransferase KYP (Kryptonite/SUVH4) [70–73]. CHH methylation is maintained by DRM2 (Domains Rearranged Methyltransferase 2), an ortholog of the mammalian *de novo* DNA methyltransferase DNMT3 [74,75]. Moreover, *DRM2* is responsible for the *de novo*

methylation of all types of cytosine contexts in *Arabidopsis* [76]. DRM2 is recruited to target loci by a specialized RNA interference pathway called RNA-directed DNA methylation (RdDM) by means of 24 nucleotide small interfering RNAs (siRNA) [77–82].

On a genome wide level, DNA methylation is controlled by the position and composition of nucleosomes and associated histone modifications [83]. The chromatin remodelers DDM1 (Decrease In DNA Methylation 1) and DRD1 (Defective In RNA-Mediated DNA Methylation 1) are important for CG methylation and non-CG methylation, respectively [84,85]. In *Arabidopsis*, DNA methylation is highest within pericentromeric regions that are enriched for transposable elements and additional repetitive DNA [67,86,87].

Approximately 5% of *Arabidopsis* genes show DNA methylation within promoter regions, where it negatively impacts transcription [67,87]. Nearly one third of *Arabidopsis* loci exhibit CG methylation within transcribed regions (so-called body-methylation that is controlled by MET1) with a bias towards the 3' half of the transcription unit [67,86–88]. Unlike promoter methylation, the biological role of body-methylation is less consistent, acting as either positive or negative effectors of gene expression [67,86].

DNA methylation is enzymatically reversible by the action of bifunctional DNA glycosylases and AP lyases [89]. ROS1 (Repressor Of Silencing 1), DML2, and DML3 (Demeter-Like 2 and 3) act in somatic cells and appear to be involved in fine-tuning of methylation levels at specific loci [90]. DME (Demeter) functions in extraembryonic tissues of seeds, the endosperm, where its activity results in a genome-wide hypomethylation and causes imprinting of the maternal genome [91–93]. DNA methylation can also be lost non-enzymatically during consecutive rounds of replication and cell divisions if factors involved in maintenance are missing, e.g. in postmeiotic cell divisions that occur during both male and female gamete development in plants [94].

2.2. Histone modifications

Histones are subject to various post-translational modifications, which control important aspects of DNA-associated processes, such as transcription, replication, chromosome condensation/segregation, as well as DNA repair. The large variety of histone modifications and their possible combinatorial effects are recapitulated by the histone code hypothesis, which states an epigenetic code affecting the transcriptional potential of a given locus [95,96].

Modifications of histones H3 and H4, especially those occurring at residues within their N-terminal tails that protrude from the nucleosome, are, to date, best understood with regard to their effects on gene regulation. Among those modifications are acetylation and methylation of histone lysine residues.

Levels of genomic histone acetylation are controlled by the antagonistic activity of a range of histone acetyltransferases (HAT) and histone deacetylases (HDAC) [97]. Histone lysine methylation is catalyzed by the SET domain of histone lysine methyltransferases (HKMT) [98,99]. HKMTs have different effects on transcriptional activity, depending on the site and mode of histone modification, reflected in mono-, di- or tri-methylation of distinct lysine residues [100]. Histone lysine methylation can be reversed by two types of histone

demethylases. The LSD1 class (lysine-specific demethylase 1) of amine oxidases acts on di- and mono-methylated lysines, whereas Jumonji C (JmjC) domain-containing proteins demethylate mono-, di- and tri-methylated lysine's by hydroxylation. Histone acetylation and methylation are involved in shaping large domains within the genome that are characterized by profound differences in their transcriptional states – eu- and heterochromatin. Euchromatin is characterized by actively expressed loci and histone modifications that correlate with active transcription. Heterochromatin, on the other hand, is enriched in repetitive sequences such as transposons, and harbors histone modifications associated with gene silencing [101].

Marks that are associated with active genes include acetylation and histone H3 lysine 4 (H3K4) methylation. H3K4me1, me2, and me3 are under-represented in repeat and transposon-rich regions of the genome and are highly enriched in genic regions [84,102]. Whereas H3K4me1 and me2 are associated with both active and inactive genes, H3K4me3 is strictly correlated with active genes and is enriched in both promoters and the 5' end of genes [102]. H3K4me3 is directed, at least in part, by ATX1 (*Arabidopsis* Thrithorax 1) [103,104].

Plant heterochromatin is characterized by cytosine methylation, hypo-acetylated histones, histone H3K9me1, H3K9me2, as well as H3K27me1 [98]. In contrast, *Arabidopsis* lacks detectable amounts of H4K20me1, which is associated with heterochromatin in mammals and yeast [96,105]. H3K9me2 in *Arabidopsis* is controlled redundantly by KYP/SUVH4, SUVH5, and SUVH6 [106–108] and controls CHG methylation [72,73,109,110]. However, H2K9me2 is also reinforced by CG methylation [60–62,111]. In contrast, H3K27me1 is not connected to DNA methylation and is controlled by ATXR5 and ATXR6 (*Arabidopsis* Trithorax-Related 5 and 6) [62,112]. Thus, H3K9me2 and H2k27me1 appear to act non-redundantly in the formation of constitutive heterochromatin.

Both H3K9 and H3K27 can be tri-methylated. While the role of H3K9me3 in gene regulation is less clear, H3K37me3 is associated with gene silencing and provides cellular memory to maintain silencing during development [105,113]. Similar to the situation described for animals, H3K27me3 is dependent on E(Z) (Enhancer Of Zeste) homologs. The *Arabidopsis* genome harbors 3 E(Z)-like proteins, CLF (Curly Leaf), MEA (Medea), and SWN (Swinger) that are components of distinct PRC2-like complexes (Polycomb Repressive Complex 2) and regulate various aspects of development, such as seed development and flowering time control [114]. Whereas in animals H3K27me3 set by PRC2 is bound by PRC1, homologs of PRC1 are missing in plants. In *Arabidopsis*, H3K27me3 is bound by LHP1 (Like Heterochromatin Protein 1), which together with other factors seems to fulfill PRC1 function [113–115].

In summary, epigenetic states of genes mediated by DNA methylation and histone modifications change in a pre-programmed fashion during plant development, and interference with epigenetic pathways often results in developmental phenotypes (for recent reviews see [58,116–118]). More recently however, roles for epigenetic changes in successful plant responses to stress conditions are becoming increasingly evident, suggesting

that epigenetic pathways have an important role in stress tolerance, acclimation, and possibly adaptation (e.g., [119,120]).

3. Coping with adverse environments

3.1. Strategies of adaptation and acclimatization

Plants regularly encounter unfavorable environmental conditions such as, temperature extremes, drought, radiation, heavy metal and salt stress, as well as exposure to pathogens and herbivores. In general, all these stresses potentially impinge on key physiological functions and could disrupt normal structures. Consequences of metabolic dysfunction, inhibition of photosynthesis, as well as damage of cellular structures, involve severe growth disturbances, reduced fertility or premature senescence [121].

Different plants species are highly variable with respect to their optimum environments. Environmental conditions that are harmful for one plant species might not be stressful for another [121,122]. Furthermore, the plant's developmental stage is important for its tolerance to adverse conditions. This is also reflected by a multitude of different stress response mechanisms that can be distinguished. Two major strategies are stress avoidance and stress tolerance [123]. Stress avoidance includes a variety of protective mechanisms that delay, restore, or prevent the negative impacts of stress. Such adaptation is shaped by selection over many generations, is stable and inherited. In contrast, stress tolerance is the potential to acclimate to stressful conditions. Acclimation is plastic and reversible. The capacity to acclimate is genetically determined but resistance gained by acclimation is not inherited and has to be reacquired by each new individual. For example, in summer, trees and herbaceous plants in northern latitudes cannot withstand freezing. However, exposure to chilling temperatures induces hardening and acclimated plants survive winter temperatures far below freezing. Such gradual exposure to environmental constraints allows for an increased resistance to various stresses including heat, saline, and drought conditions. However, the physiological modifications induced during acclimation are usually lost when the adverse environmental conditions do not persist [121].

3.2. Mechanisms of plant stress responses

Plant stress responses are highly dynamic and involve complex crosstalk between different regulatory levels. Responses can be short-lived, like metabolic modifications, or quite persistent as, for example, morphogenic adjustments. Ongoing research has revealed that different environmental constraints trigger a common set of cellular, biochemical, and molecular responses, as well as stress-specific processes. Clearly, such a multitude of stress-induced responses needs to be delicately coordinated by integrated signal transduction systems that both crosstalk and provide specificity to particular environmental requirements [124,125].

Cellular responses to stress include changes in cell cycle and cell division, adjustments of membrane composition, and modifications of the cell wall architecture. Furthermore, plants alter metabolism in various ways, including production of compatible solutes such as proline, raffinose, and glycine betaine for osmotic adjustment and redox metabolism to remove excess levels of ROS (reactive oxygen species) and to reestablish cellular redox

balance [122,126–128]. At the molecular level, gene expression, including transcription, RNA splicing, stability and translation, is adjusted in response to stress[129–133]. Stress-inducible genes comprise genes involved in direct protection from stress and genes that encode regulatory proteins. The first group includes genes involved in the synthesis of osmoprotectants, detoxifying enzymes, and transporters, whereas the latter comprises genes encoding transcription factors, protein kinases, and phosphatases.

3.3. Epigenetic regulation of stress responses

In addition to canonical stress signaling pathways, dynamic responses to environmental fluctuations seemingly involve epigenetically controlled pathways that impinge on genome stability [134]. This is well documented by Barbara McClintock's pioneering work on stress-induced instability of transposons in maize, and similar effects have been observed in other plant species [47,135,136] (Table 2). Furthermore, a number of reports have described alterations in the frequency of homologous recombination following exposure of plants to a variety of agents [137–140]. In *Arabidopsis*, for example, various abiotic stresses were shown to cause increased genomic instability and higher frequencies of homologous recombination events [51,141–144] (Table 2).

Some of these environmental effects show a correlation with alterations in DNA methylation and the establishment of epialleles[138,145–151]. In snapdragon, for example, low temperature causes activation of transposon Tam3, which correlates with diminished DNA methylation [152,153]. Similarly, periods of low temperature that modulate vernalization in plants correlate with adjustments in DNA methylation [154–156]. Circumstantial evidence for a role of environmentally-induced epialleles in the mediation of adaptive stress responses became apparent when testing chemically induced DNA hypomethylation in rice, which conferred an adaptive advantage against the pathogen *Xanthomonas oryzae* [157]. Moreover, when analyzing *Arabidopsis* recombinant inbred lines deficient in key regulators of DNA methylation, over several generations, a range of inherited phenotypes, including altered responsiveness to biotic and abiotic stressors, has been identified [158,159]. These effects could relate to the observation that mutants defective in DNA methylation, or in the control of chromatin structure or DNA repair, exhibit a higher reactivation frequency of transcriptionally silenced loci [160–164]. Thus, stress-induced variations in DNA methylation and the establishment of epialleles appear to represent an effector in stress signaling that, in one way or another, modulate the spectrum of responses that define the adaptive capacities in plants [138,145–151]. It has to be pointed out that alterations in DNA methylation at silenced loci do not necessarily represent a universal prerequisite for stress-mediated reactivation of transcriptionally silent loci [50,144]. Notably, *Arabidopsis* chromatin remodeling proteins appear to be involved in the resilencing of stress-induced loci, suggesting that deficiencies in the dynamic control of chromatin organization feed back on the epigenetic status of stressed plants [50,144]. Furthermore, adverse environmental conditions trigger post-transcriptional regulatory networks including homology based control of mRNA stability and translation through short non-coding sncRNAs and via RNA interference, RNAi [57,84,165–170]. A strong candidate for a non-coding RNA involved in epigenetic regulation of stress responses was identified in the resurrection plant

Craterostigma plantagineum. This particular sncRNA has a close similarity to SINE-like retrotransposons and negatively regulates desiccation-tolerance genes [171,172].

Clearly, it remains to be determined how all these distinct components of the epigenetic machinery might interact to contribute to an adjustment of stress responsiveness in plants.

3.4. Stress enhances transgenerational epigenetic effects

Although Barbara McClintock correctly predicted that transposons have heritable but reversible transitions between active and inactive states it took until the late 1980s to correlate transposition activity with variation in DNA methylation that are transmitted to the next generation [173–179]. Since then, several, sometimes conflicting, reports have suggested that biotic and abiotic stressors are able to perturb the fidelity of epigenetic marks, thereby increasing the frequency of transgenerational epigenetic effects in unstressed progeny of stressed plants (Table 2). Most often, these changes appear to affect specific loci such as repetitive DNA, transposons, and transgenes, but only in a few cases effects on expression of structural genes have been observed [180]. A severe limitation in the analysis of such events relates to the often highly stochastic characteristic of epigenetic responses, affecting limited numbers of somatic cells. To address this bottleneck, several reporter lines have been generated that mark cells that have undergone somatic homologous recombination [139,181,182] or reactivation of a transcriptional silenced transgene [183–185].

Frequencies of stochastic epigenetic alterations appear to be influenced by growth conditions, time, and duration of stress application, but also by the experimental setup of material sampling and scoring (Table 1). For example, exposure of *Arabidopsis* to UV-C radiation and to the bacterial elicitor flagellin increased the frequency of somatic homologous recombination significantly in up to four progeny generations after stress application [48]. These findings were challenged by another study in which effects of 10 different physical and chemical stressors on somatic homologous recombination frequency were presented [51]. The authors found that most stressors induced a higher frequency of somatic homologous recombination shortly after stress exposure. However, effects were only significant for a subset of these stressors [51]. In contrast, Boyko et al. [186] found that Cl^- ions caused a significant heritable increase in the frequency of somatic recombination and DNA strand breaks. Furthermore, these plants seemingly developed a higher tolerance to salt stress, possibly as a result of accurate DNA surveillance and repair mechanisms. In another study [50] demonstrated that extreme temperatures and variable exposure to UV-B radiation caused a heritable increase in the reactivation of a transcriptionally silenced reporter locus. Related observations were made in the apomictic species *Taraxacum officinale* (Dandelion), in which biotic and abiotic stress regimes caused heritable alterations in genome-wide DNA methylation [187].

Together with additional studies, these observations highlight heritable effects of stressful environments on the epigenetic status of plants, which in some cases were suggested to feed back on the fitness of stressed populations. In tobacco, for example, infection with tobacco mosaic virus (TMV) resulted in elevated recombination frequencies and hypomethylation of several pathogen resistance loci that might account for an increased resistance to a range of

pathogens in the progeny of originally infected tobacco plants [49,188]. Similar fitness effects have been described for *Arabidopsis* plants exposed to elevated temperatures that remained detectable for two generations after stress treatment [189].

3.5. Mechanisms driving transgenerational inheritance of epigenetic states

A general mechanism postulated to restrict transmission of acquired epigenetic states between generations involves establishment of a default epigenetic status during gametogenesis and early phases of embryo development. Extensive DNA demethylation has been reported in pollen and the endosperm [91,92,190–192]. Furthermore, it could be [193–195] demonstrated that histone H3 marks in male and female gametes, as well as in the zygote, are changed in a replication-independent manner.

Given the increasing number of examples for transgenerational epigenetic inheritance it seems likely that some epigenetic marks escape their erasure during gametogenesis and fertilization. Alternatively, they might be replaced by other marks, or memorized by the action of other molecules such as small non-coding RNAs [196]. Such responses were demonstrated to be active in mammals [197], in which subsets of nucleosomes, associated with epigenetic marks, are retained in sperm cells [198]. In plants, *Arabidopsis* mutants defective in CG methylation, exhibit stable inheritance of numerous hypomethylated loci for at least eight generations after outcrossing of the mutant alleles [158,159]. Notably, such induced DNA hypomethylation appears to revert over several generations in an RNAi-dependent manner [159,199]. This kind of epigenetic resetting resembles the progressive inactivation of transposable elements in maize, and the silencing of transgenic loci in many plants [200,201]. Further evidence for involvement of small non-coding RNAs in memorizing epigenetic changes comes from the analysis of *Arabidopsis* plants deficient for Dicer-like 2 (DCL2) and Dicer-like 3 (DCL3), as such mutants were not able to properly establish transgenerational stress effects on the frequency of somatic homologous recombination [202].

siRNA is present in male and female gametes, thus potentially allowing for either RdDM or post-transcriptional silencing of specific loci during gametogenesis, via modulation of *de novo* methylation in sperm cells as well as in the zygote [190–192,203]. This would be consistent with observations pointing towards transgenerational inheritance of stress effects on epigenome stability via both types of gametes [50]. On the other hand, Boyko and Kovalchuk [204] reported transmission of stress effects predominantly through the female gametophyte.

Results obtained by numerous groups provide a strong case for heritable stress effects on the epigenetic status of higher plants. Yet, it remains to be determined whether or not all these effects are the result of a stochastic relaxation of epigenome stability. Alternatively, some of the observed responses might arise as a consequence of biased variations in the accuracy of specific regulatory pathways that, as an ultimate consequence, offer a selective advantage under specific environmental conditions. Another issue that remains to be addressed involves the long-term consequences of less stringent control of epigenome stability. Obviously, accumulative formation of stable and metastable epialleles in the progeny of stressed plants could negatively impact on plant fitness. Thus, plants need to somehow

restrict stress effects on epigenome stability. Evidence for the operation of resetting mechanisms that antagonize stress effects on epigenome stability during seed aging has been provided in a recent study [50]. Nevertheless, whether this response involves activity of specific ‘resetting pathways’ or alternatively, arises as the result of a stochastic loss of stress-induced epigenome adjustments, remains to be determined.

3.6. Epigenetic marks and their impact on mutation frequencies

Global and local changes in epigenetic marks are suggested to result in a ‘genomic shock’ reflected in an increased frequency of mutagenic events that impinge on genome integrity [138]. A biological relevance for crosstalk between epigenetic variability and stable genetic changes becomes apparent when assessing potential effects over multiple generations on an evolutionary scale. This involves, for example, mutagenic consequences of reactivation of silenced transposons upon adjustments of epigenetic marks. Similarly, elevated levels of cytosine methylation appear to increase mutation frequencies owing to elevated levels of cytosine-to-thymine transitions, further highlighting a close interrelationship between epigenetic and genetic inheritance [205,206]. Furthermore, conformational variations in DNA and chromatin could actively control genome integrity. DNA in a less condensed, open chromatin conformation is more accessible to mutagens, DNA repair, and recombination systems, whereas condensed chromatin decreases the probability of mutations. This implies that alterations in chromatin conformation and DNA accessibility brought about by dynamic alterations in epigenetic marks could drive spatiotemporal variations in genome mutability. Thus, in addition to reversible adjustments in the activity or expression levels of a wide range of loci, environmentally induced adjustments of a plant’s epigenetic status, might also affect correlated genetic variations thereby corroborating and accelerating mechanisms of adaptive evolution.

4. Outlook

To date only few examples of transgenerational epigenetic inheritance have been reported in plants. Although knowledge about the possible mechanisms is steadily emerging, there are still many open questions. However, understanding transgenerational epigenetic inheritance might be the answer to several questions regarding adaptation.

Recent studies on epigenetic variations between populations, individual organisms, and upon different environmental conditions, suggest their importance for phenotypically relevant adaptations [65,66,207]. The emerging theme is that epigenetic mechanisms buffer developmental programs and at the same time maintain plasticity. Periodic breakdown of this epigenetic buffering potentially causes increased phenotypic variations that might be a future source for increasing the variability in germplasm. Thus, for example, the increase and identification of heritable epigenetic phenotypes could enhance the efficiency of breeding programs. To understand the evolutionary dynamics and responses to ecological adaptations, mathematical models have recently been proposed that combine information on the probability of transmission of ancestral phenotypes, the number of epigenetic reset opportunities between generations, and assumptions on the environmental induction of epigenetically regulated traits ([208]). These models will facilitate the identification of the

heritable epigenetic variance and transmissibility for future molecular studies such as genome wide association and QTL studies.

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Table 1

Impact of variations in the epigenetic status on plant growth and development.

Plant species	Induction	Epigenetic status	Effect	Reference
<i>Oryza sativa</i> DWARF1		DNA hypomethylation	Growth	[209,210]
Wheat <i>Triticum aestivum</i>	Glutenin gene	DNA methylation		[211]
Triticale		Hypomethylation	Induced growth	[212]
Tobacco <i>Nicotiana tabacum</i>	Transgenesis	Loss of expression of transgene, hypermethylation of T-DNA	Transgene silencing	[213]
Arabidopsis	Transgenesis	Loss of expression of <i>hpt</i> transgene	Hygromycin sensitivity	[214]
Petunia	Transgenesis	Loss of expression of transgene, hypermethylation of T-DNA		[215]
Arabidopsis AGAMOUS	<i>met1</i> , <i>ddm1</i> background	DNA hypermethylation	Floral organ development, patterning	[216,217]
<i>Silene latifolia</i>	5-azacytidine	DNA hypomethylation	Sex change to androhermaphroditism	[218]
Arabidopsis SUPERMAN/clark kent	<i>met1</i> , <i>ddm1</i> background	DNA hypermethylation	Floral organ development, patterning	[219,220]
Arabidopsis PAI (phosphoribosylanthranilate isomerase)	Natural	Ecotypes with hypermethylated multiplied PAI genes, result in the silencing of the unlinked PAI genes	PAI2 silencing results in blue fluorescing plants	[221–224]
<i>Linaria vulgaris</i> LCYCLOIDEA	Natural	Cytosine DNA methylation of glutenin genes	Floral development	[36]
Arabidopsis FLOWERING WAGENINGEN (FWA)	Natural	Loss of methylation, ectopic expression of FWA	Late flowering	[225]
Arabidopsis <i>BALICPR1</i> (constitutive expressor of <i>PR</i> genes 1)	<i>ddm1</i> background	Overexpression of CPR1	Twisted, leaves, dwarfing and reduced fertility	[226]
Arabidopsis Flowering Repressor Locus (FLC)	Natural	H3K9 and H3K27 dimethylation at FLC locus after vernalization	Flower induction after vernalization	[227,228]
Flax <i>Linum usitatissimum</i>	5-azacytidine	DNA hypomethylation, chromatin remodeling	Number of leaves, flowering age, stem height	[229,230]
Flax <i>Linum usitatissimum</i>	Nutrient conditions, heat	DNA methylation, presence of insertion element	Biomass, growth	[136]
Tomato	Natural	SBP-Box gene	Fruit ripening	[231]
Arabidopsis	Natural	Non-LTR retrotransposon Sadhu is differentially expressed in natural accessions as Col (active), Cvi and Ler (inactive)		[232]
Arabidopsis BONSAI	<i>ddm1</i> background	DNA hypermethylation and silencing of APC13/BNS gene by nearby a long interspersed	Growth	[233]

Plant species	Induction	Epigenetic status	Effect	Reference
Melon <i>Cucumis myriocarpus</i>	Natural transposon insertion	Spreading of DNA methylation to WIP1 promoter	Sex determination, expression of WIP1 leads to carpel abortion	[234]
Wild potato <i>Solanum ruiz-lealii</i> Brück.	Species of hybrid origin	Phenotypic instability of flower development	Flower development	[235]

Table 2

Heritable stress effects on genome and epigenome stability in plants.

Plant species	Growth conditions	Read-out	Effect	Number of generation	Reference
Maize	Biotic and abiotic stress	Transposon activation	Corn pigmentation, variegation		[47]
Tobacco	Infection with tobacco mosaic virus, oilseed rape mosaic virus	Homologous recombination	Increased frequency of homologous recombination	One generation after infection	[145]
Arabidopsis	UV-C flagellin	Transgenic lines for histochemical visualization of homologous recombination	Homologous recombination increases	Four generations after stress exposure	[48]
Tobacco	Tobacco mosaic virus infection		Increased homologous recombination, global hypermethylation, local hypomethylation, increased resistance to viral, bacterial and fungal pathogens	One generation after infection	[149,188]
Arabidopsis	10 different physical and chemical stress treatments on in vitro cultivated seedlings	Two independent homologous recombination reporter lines	Homologous recombination increased mostly in the stressed generation, highest response by compounds that modify or damage DNA	One generation after stress with mannitol, heat, paraquat, zebularin, UV-C, bleomycin, two generations after stress with mannitol, zebularin, UV-C, NaCl	[51]
Arabidopsis	Heat, cold, UV-B on soil cultivated 2–3 week old plants	Reactivation of transcriptionally silenced (TS-GUS) reporter line, activation of retrotransposons	Increased frequency of TS-GUS reactivation, increased transcription of retrotransposons	Frequency of TS-GUS reactivation increased in two generations after stress exposure, inherited through both alleles and in trans, counterbalanced by seed aging	[50]
Arabidopsis	NaCl, MgCl ₂ , KCl with in vitro cultivated seedlings	Homologous recombination reporter lines	Increased frequency of homologous recombination	One generation after stress exposure, higher tolerance to NaCl and genotoxic (methyl methane sulfate) treatments	[186]
Arabidopsis, <i>dcl2</i> , <i>dcl3</i> , <i>dcl4</i>	NaCl, UV-C, cold, heat flooding	Homologous recombination	Higher homologous recombination frequency, increased global genome	One generation, increased homologous recombination of the progeny of UV-C	[202]
Arabidopsis	Heat, cold	Fitness (seed production per individual)	Increased fitness upon heat exposure	Two generations after heat exposure	[189]
Arabidopsis	UV-C, heat, cold, drought, flood	Marker lines for homologous recombination, point mutation, small deletions	Increased frequency of homologous recombination after heat, cold, flood and UV-C stress — but not drought	First generation after UV-C frequency of homologous recombination increased	[236]
Dandelions (apomictic) <i>Taraxacum officinale</i>	Low nutrients, NaCl, jasmonic acid, salicylic acid	DNA methylation, MS-AFLP	Highly significant methylation changes (gain and loss) at AFLP markers upon SA treatment, lower significance for the other treatments	One generation after stress exposure	[187]