

Evolution and function of genomic imprinting in plants

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Genomic imprinting, an inherently epigenetic phenomenon defined by parent of origin-dependent gene expression, is observed in mammals and flowering plants. Genome-scale surveys of imprinted expression and the underlying differential epigenetic marks have led to the discovery of hundreds of imprinted plant genes and confirmed DNA and histone methylation as key regulators of plant imprinting. However, the biological roles of the vast majority of imprinted plant genes are unknown, and the evolutionary forces shaping plant imprinting remain rather opaque. Here, we review the mechanisms of plant genomic imprinting and discuss theories of imprinting evolution and biological significance in light of recent findings.

Genomic imprinting is defined by biased expression of a gene from one allele over the other based on the sex of the parent that contributed the allele. As such, biased expression can occur even when both alleles have identical DNA sequences. A gene that is predominantly expressed from the maternally inherited allele is referred to as a maternally expressed imprinted gene, whereas a gene that is expressed from the paternally inherited allele is referred to as a paternally expressed imprinted gene. The implication for both types of imprinted genes is that maternally and paternally inherited alleles are differentiated post-fertilization by a pre-existing mark that is epigenetic or, in other words, not directly encoded by the DNA sequence. This epigenetic mark is referred to as the “imprint” for the imprinted gene (Fig. 1).

Although evidence of genomic imprinting was observed by mule breeders long before the development of modern genetics, the phenomenon was not formally described in plants and mammals until relatively recently (Morison and Reeve 1998). The present concept of genomic imprinting began to take shape as a result of genetic experiments in maize, which demonstrated that the *R* pigmentation gene is preferentially expressed when inherited from the mother (Kermicle 1970). Subsequent experiments in

plants and mammals demonstrated that the paternal and maternal genomes are epigenetically distinct (Bartolomei and Ferguson-Smith 2011; Pires and Grossniklaus 2014) and led to the identification of the first mammalian imprinted genes (Barlow et al. 1991; Bartolomei et al. 1991; DeChiara et al. 1991). Further studies elucidated the mechanisms of imprinting and the functions of several imprinted genes (Huh et al. 2008; Ferguson-Smith 2011).

For a mammalian locus to be imprinted, epigenetic marks set up before the formation of the zygote (Lucifero et al. 2004; Kato et al. 2007; Kobayashi et al. 2013), referred to as primary imprints (Fig. 1; Barlow 1994), must escape chromatin reshaping mechanisms in the embryo (Mayer et al. 2000; Oswald et al. 2000; Proudhon et al. 2012). Parent of origin-dependent epigenetic differences may also appear in the zygote or later stages once maternally and paternally inherited chromosomes are in the same nucleus (Tomizawa et al. 2011). Such secondary or somatic imprints rely on the presence of a primary imprint (Fig. 1; Ferguson-Smith 2011).

The logic of genomic imprinting in flowering plants is similar but has to be adjusted for the unique mechanism of plant reproduction. The haploid products of plant meiosis do not directly differentiate into gametes but instead divide mitotically several times to form multicellular gametophytes (Fig. 2). The male gametophyte, pollen, contains two sperm cells and a vegetative cell, which forms a pollen tube that delivers the sperm cells to the female gametophyte (Fig. 2). In flowering plants, one of these fuses with the egg to form the zygote, and the other fuses with the central cell, which is usually homodiploid, to form the triploid endosperm (Fig. 2), a transient seed tissue with nutritive and supportive functions analogous to the mammalian placenta. Although the two sperm cells are morphologically distinct in some plants, they appear to be at least somewhat functionally interchangeable (Russell 1991; Faure et al. 2003), suggesting that differential imprinting between the sperm cells is unlikely. Flowering plants therefore have three cell types (sperm,

[*Keywords:* DNA methylation; epigenetics; evolution; genomic imprinting; histone methylation; plant reproduction]

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Article is online at <http://www.genesdev.org/cgi/doi/10.1101/gad.269902>.
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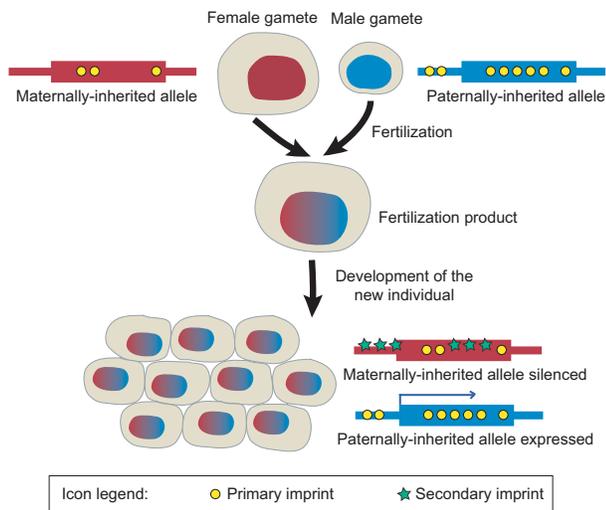


Figure 1. Imprinted gene expression. Maternally and paternally inherited alleles are epigenetically distinguished (or imprinted), causing differential expression in the fertilization product. Primary imprints are established before fertilization, whereas secondary imprints are guided by primary imprints after fertilization.

egg, and central cells) in which primary imprints can be established, with maternal imprints potentially quite different between the central and egg cells. Studies of individual plant imprinted genes (Chaudhuri and Messing 1994; Grossniklaus et al. 1998; Kinoshita et al. 1999, 2004; Luo et al. 2000; Danilevskaya et al. 2003; Gutier-

rez-Marcos et al. 2004, 2006; Kohler et al. 2005; Baroux et al. 2006; Gehring et al. 2006; Jullien et al. 2006a; Haun et al. 2007; Hermon et al. 2007; Makarevich et al. 2008; Tiwari et al. 2008; Fitz Gerald et al. 2009) and subsequent genome-scale investigations that identified hundreds of imprinted genes in *Arabidopsis thaliana*, castor bean, rice, and maize (Gehring et al. 2011; Hsieh et al. 2011; Luo et al. 2011; Waters et al. 2011, 2013; Wolff et al. 2011; Zhang et al. 2011, 2014; Pignatta et al. 2014; Xu et al. 2014) have indeed demonstrated that the bulk of plant imprinted expression occurs in the endosperm, whereas imprinting in the embryo is rare and transient (Jahnke and Scholten 2009; Autran et al. 2011; Hsieh et al. 2011; Luo et al. 2011; Nodine and Bartel 2012; Raissig et al. 2013; Pignatta et al. 2014). These studies also established DNA methylation as the most prevalent primary imprint (Fig. 3). Trimethylation of Lys27 of histone H3 appears to be a common secondary imprint, particularly at paternally expressed genes, but may also serve as the primary imprint at some genes (Fig. 3).

Although hundreds of plant imprinted genes have been identified and much progress has been made in elucidating the epigenetic mechanisms that regulate them, the biological significance of plant imprinting remains mysterious, and the evolutionary forces that led to the emergence of imprinting have been extensively debated. In this review, we summarize the current knowledge about the mechanisms of plant imprinting and discuss the evolutionary theories and potential functional consequences of this epigenetic process.

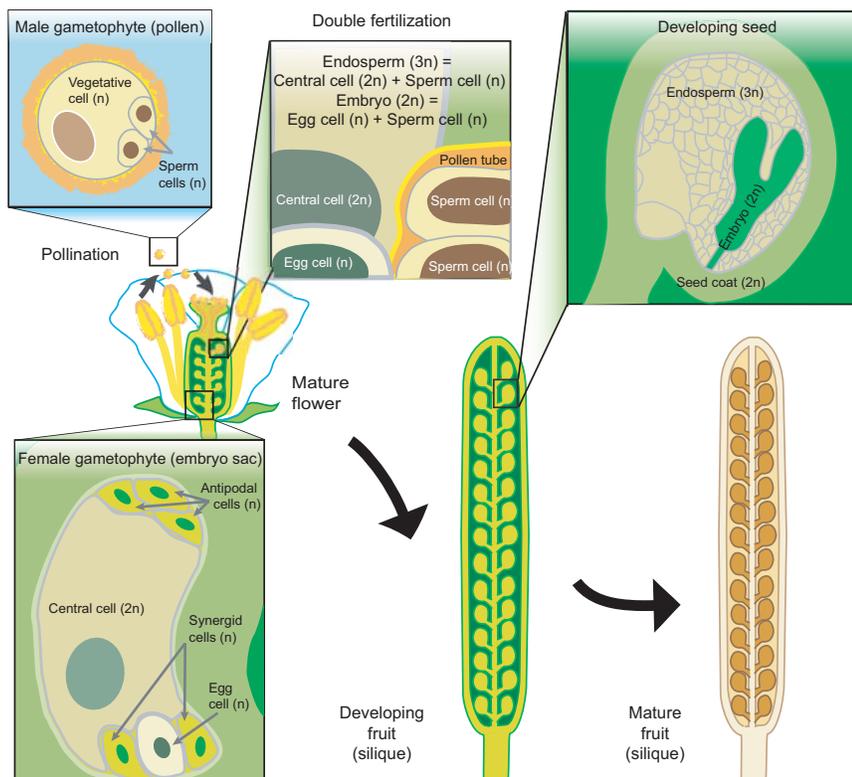


Figure 2. Sexual reproduction in the flowering plant *A. thaliana*. The gametes are contained within multicellular haploid structures called gametophytes that are derived by mitosis from meiotic spores. The fusion of two haploid polar nuclei forms a diploid central cell in the female gametophyte. At the time of fertilization, the diploid female central cell and a haploid male sperm cell fuse to give rise to the endosperm, while the haploid female egg cell and haploid male sperm cell fuse to give rise to the embryo. The resulting seed is formed of the endosperm, the embryo, and a maternally derived seed coat.

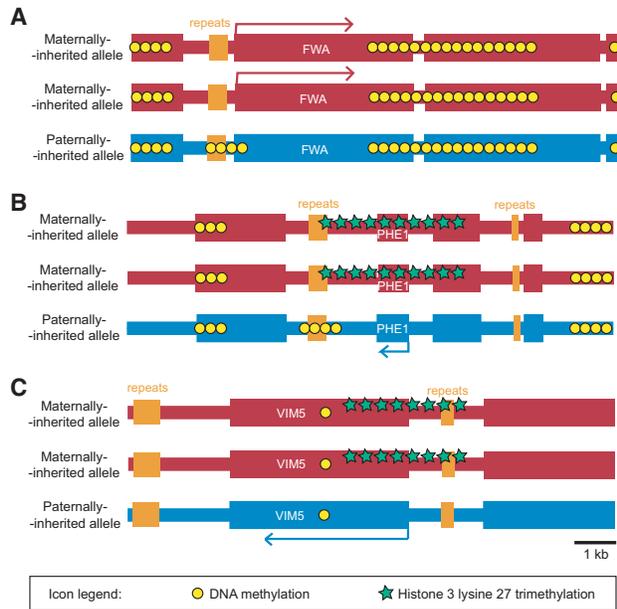


Figure 3. Mechanisms of imprinting in the endosperm of flowering plants. (A) At the *Arabidopsis* *FWA* locus, DEMETER (DME) activity at upstream repeats, presumed to occur in the central cell but not the sperm cells, forms a primary imprint that results in maternal-specific expression. (B) The primary imprint at the *Arabidopsis* *PHERES1* gene is also formed by presumed central cell-specific demethylation of repeats by DME. Loss of methylation at these repeats results in histone 3 Lys27 trimethylation. This secondary imprint laid down by polycomb-repressive complex 2 (PRC2) causes silencing of the maternal loci and paternal-specific expression. (C) *Arabidopsis* *VIM5* is an example of a gene that does not appear to rely on DME-mediated DNA demethylation for the formation of the primary imprint, as both maternal and paternal alleles are deficient in DNA methylation. Instead, histone 3 Lys27 trimethylation may form a primary imprint that results in paternal-specific expression (Hsieh et al. 2011).

Epigenetic mechanisms of genomic imprinting

Imprinting mechanisms have been extensively reviewed in mammals (Barlow 2011; Bartolomei and Ferguson-Smith 2011; Ferguson-Smith 2011; Adalsteinsson and Ferguson-Smith 2014; MacDonald and Mann 2014) and plants (Bauer and Fischer 2011; Raissig et al. 2011; Kohler et al. 2012; Gehring 2013; Zhang et al. 2013). We therefore keep the discussion of imprinting mechanisms fairly brief.

DNA methylation

DNA methylation is a classic mechanism of epigenetic inheritance. The most prominent type of eukaryotic DNA methylation is catalyzed by enzymes of the Dnmt1 family, called MET1 in plants (Feng et al. 2010; Law and Jacobsen 2010; Zemach et al. 2010b). These enzymes catalyze methylation of cytosines within symmetric CG dinucleotides when a cytosine on one of the DNA strands is already methylated, thereby perpetuating methylation patterns following DNA replication. DNA methylation

is classically associated with the silencing of genes and transposable elements but can also promote gene activity (Makarevich et al. 2008; Shibuya et al. 2009; Jones 2012; Rigal et al. 2012; Deng and Chua 2015; Lei et al. 2015; Williams et al. 2015). Consequently, differential methylation of maternal and paternal alleles can cause imprinted expression (Fig. 3).

DNA methylation was the first imprint discovered in mammals (Bartolomei et al. 1993; Ferguson-Smith et al. 1993; Stoger et al. 1993) and in plants (Kinoshita et al. 2004) and is still the only differential mark known to be established as a primary imprint (Dickinson and Scholten 2013; MacDonald and Mann 2014). All identified parent of origin-specific DNA methylation differences in the endosperm of *Arabidopsis*, rice, and maize are due to site-specific hypomethylation of maternally inherited DNA (Waters et al. 2011; Zhang et al. 2011, 2014; Ibarra et al. 2012; Rodrigues et al. 2013). In *Arabidopsis*, this hypomethylation is catalyzed by the DEMETER (DME) DNA glycosylase, which can excise methylated cytosine from DNA (Gehring et al. 2006; Ibarra et al. 2012). DME is presumed to act in the female central cell prior to fusion with the sperm (Fig. 2; Choi et al. 2002).

DNA demethylation by DME has been associated with both maternal-specific gene activation (Kinoshita et al. 2004; Gehring et al. 2006; Hsieh et al. 2011; Ibarra et al. 2012) and maternal-specific gene repression (Makarevich et al. 2008; Hsieh et al. 2011; Ibarra et al. 2012). In maize and rice, maternal-specific DNA hypomethylation reminiscent of DME activity likewise occurs at maternally and paternally expressed imprinted genes (Gutierrez-Marcos et al. 2006; Haun et al. 2007; Hermon et al. 2007; Waters et al. 2011; Zhang et al. 2011, 2014; Rodrigues et al. 2013). Furthermore, maternally and paternally expressed genes show distinct patterns of demethylation that are similar between *Arabidopsis*, maize, and rice (Ibarra et al. 2012; Rodrigues et al. 2013; Zhang et al. 2014), suggesting that the locations of regulatory regions that govern activation and repression have been generally conserved across 150 million years of evolution (Chaw et al. 2004). The regulatory importance of DNA methylation is supported by evidence that perturbations of methylation patterns at individual genes abolish imprinting (Adams et al. 2000; Xiao et al. 2003; Kinoshita et al. 2004; Jullien et al. 2006b; Makarevich et al. 2008; Hsieh et al. 2011; Vu et al. 2013; Du et al. 2014). However, not all imprinted genes are clearly associated with endosperm-specific maternal DNA hypomethylation (Hsieh et al. 2011; Waters et al. 2011; Wolff et al. 2011; Zhang et al. 2011, 2014; Xu et al. 2014), suggesting either that the initial imprint is due to a yet to be discovered mechanism or that epigenetic states of parental alleles for these loci in the endosperm are poor representatives of the primary imprints present in gametes (Raissig et al. 2011).

In addition to its activity in the central cell, DME is also expressed in the pollen vegetative cell (Fig. 2; Schoft et al. 2011). DME demethylates a largely overlapping set of thousands of transposable elements in the central and vegetative cells, most of which are located far from genes and do not appear to influence gene expression (Gehring

et al. 2009; Hsieh et al. 2009; Calarco et al. 2012; Ibarra et al. 2012). The vegetative cell is terminally differentiated and does not fuse with any female gametes, so the function of DME is clearly not confined to the generation of primary imprints. Instead, DME-mediated demethylation of transposons in the central and vegetative cells is proposed to generate mobile small RNA (sRNA) molecules that direct methylation of cognate transposons in the egg and sperm cells (Hsieh et al. 2009; Slotkin et al. 2009; Schoft et al. 2011; Calarco et al. 2012; Ibarra et al. 2012), thus reinforcing the silencing of transposons in the gametes. Similar transposons are also extensively hypomethylated in rice endosperm (Zemach et al. 2010a; Rodrigues et al. 2013), suggesting that transposon demethylation is a conserved feature of flowering plant sexual development. The sites of demethylation that regulate imprinted genes are commonly transposons or other repeats (Fig. 3A,B; Kinoshita et al. 2007; Gehring et al. 2009; Villar et al. 2009; Ibarra et al. 2012; Pignatta et al. 2014), indicating that imprint formation by DNA demethylation evolved from a transposon-directed silencing mechanism (Kim and Zilberman 2014). However, at least in rice endosperm, maternal-specific DNA hypomethylation of the transcribed regions of active genes is common and is strongly associated with paternally biased expression (Rodrigues et al. 2013). This suggests that demethylation that primarily regulates gene activity may have evolved in at least some plant lineages.

Histone variants

The core histones that form the protein component of the nucleosome can be differentiated into subtypes or variants with distinct structures and functions (Talbert and Henikoff 2010). Histone variants have not yet been implicated in plant imprinting, but the specific incorporation of a particular histone H3 variant in *Arabidopsis* sperm cells (Ingouff et al. 2007) might distinguish the paternal allele in the endosperm or zygote.

Histone modification

Trimethylation of Lys27 of histone H3 (H3K27me3), catalyzed by polycomb-repressive complex 2 (PRC2), is the only histone modification known to correlate with imprinting in flowering plants (Kohler et al. 2005; Baroux et al. 2006; Gehring et al. 2006; Jullien et al. 2006a; Makarevich et al. 2008; Du et al. 2014; Zhang et al. 2014). Mutation of PRC2 disrupts the imprinting of many genes, most of which are paternally expressed (Hsieh et al. 2011; Wolff et al. 2011), with H3K27me3 of maternally inherited alleles correlating with DNA hypomethylation (Fig. 3B; Makarevich et al. 2008; Weinhofer et al. 2010). Perturbations of DNA methylation at some of these genes result in a loss of imprinting (Xiao et al. 2003; Makarevich et al. 2008; Hsieh et al. 2011; Du et al. 2014), suggesting that DNA methylation is the primary imprint that causes differential recognition by PRC2. Consistent with this, PRC2 activity is generally anti-correlated with DNA methylation, including in the *Arabidopsis* endosperm,

where PRC2 targets transposons associated with DME-mediated demethylation (Weinhofer et al. 2010; Deleris et al. 2012; Makarevitch et al. 2013; Jermann et al. 2014).

However, this mechanism cannot account for PRC2-mediated regulation of the maternally expressed *Arabidopsis* genes *MEDEA* and *AtFH5* (Baroux et al. 2006; Gehring et al. 2006; Jullien et al. 2006a; Fitz Gerald et al. 2009), which involves silencing of the paternal allele. Furthermore, some imprinted genes regulated by PRC2 are not marked by DNA methylation (Hsieh et al. 2011; Wolff et al. 2011; Zhang et al. 2014). For example, imprinting of a *MEDEA* transgene does not require DME or DNA methylation (Wohrmann et al. 2012). It is currently unclear whether H3K27me3 serves as the primary imprint at such genes, but PRC2-mediated silencing does have the requisite features. There is strong evidence that PRC2-catalyzed H3K27me3 is inherited after DNA replication and recruits PRC2, creating a self-reinforcing loop (Hansen et al. 2008; Margueron et al. 2009; Xu et al. 2010). This enables PRC2-mediated silencing of one allele while the other remains active in the same nucleus even without differentiating DNA methylation (Berry et al. 2015). Recruitment of PRC2 in the central cell or sperm—for example, by cell-specific transcription factors—could thus plausibly establish an allele-specific silent state that can be inherited by the endosperm. Unlike DME-catalyzed DNA demethylation, this mechanism could account for imprinted gene expression in the embryo (Raissig et al. 2013).

Long noncoding RNA

Imprinted long noncoding RNAs have been observed in rice and maize (Luo et al. 2011; Zhang et al. 2011). Although these molecules have not been shown to be necessary for imprinted expression of protein-coding genes, they are of potential interest because PRC2-mediated histone methylation can be targeted by long noncoding RNA in plants and animals (Heo and Sung 2011; Brockdorff 2013; Csorba et al. 2014).

sRNA

As mentioned above, sRNA molecules, particularly those that are 24 nucleotides (nt) long, target DNA methylation in plants (Matzke and Mosher 2014). DNA methylation directed by sRNA is required for imprint creation at some loci that are demethylated in the central cell (Vu et al. 2013). More generally, the role of sRNAs in imprint formation and silencing of imprinted regions is currently poorly understood. Large populations of maternally biased 24-nt sRNAs were reported in young *Arabidopsis* seed (Mosher et al. 2009), and some of these were implicated in regulating transcription factor dosage in endosperm (Lu et al. 2012). However, many of these apparently maternally biased sRNAs might originate in the maternally derived seed coat, which lies in close proximity to the *Arabidopsis* endosperm (Pignatta et al. 2014), possibly explaining why their maternal bias is unaffected by mutations in DNA- and histone-modifying enzymes that are

known to regulate imprinted gene expression (Mosher et al. 2011). A strong overabundance of maternally biased endosperm sRNAs has also been reported in maize (Xin et al. 2014) but not in rice, where maternally expressed sRNAs are equally common (Rodrigues et al. 2013). Some of these sRNAs are associated with the silenced alleles of imprinted genes, as is the case for paternally biased *Arabidopsis* sRNAs (Pignatta et al. 2014). Rice imprinted sRNAs are enriched for maternal DNA hypomethylation (Rodrigues et al. 2013), suggesting that their imprinting shares regulatory mechanisms with protein-coding genes.

The intriguing correlations between sRNAs and imprinted genes notwithstanding, it is unclear whether gene-associated imprinted sRNAs are a cause or result of imprinted gene expression, and most imprinted genes are not associated with imprinted sRNAs (Rodrigues et al. 2013; Pignatta et al. 2014; Xin et al. 2014). It is also unclear how parent of origin-specific differences in gene expression persist despite the production of *trans*-acting sRNAs that can, in theory, silence both alleles. A possible explanation is that low expression of DNA methyltransferases (Jullien et al. 2012) or other RNA-directed DNA methylation pathway genes (Belmonte et al. 2013) in the young endosperm of *Arabidopsis* renders sRNAs less effective at inducing silencing. The low levels of sRNA-mediated DNA methylation observed in rice endosperm (Zemach et al. 2010a) are consistent with this idea. Because sRNA-directed methylation is a self-reinforcing process (Kim and Zilberman 2014), it is expected to work less efficiently in *trans*, so that activity in the central cell and early endosperm may be predominantly in *cis*. It is also possible that imprinted sRNAs and gene transcripts are present in distinct compartments of the endosperm.

Mechanisms underlying the evolution of plant imprinted genes

As discussed above, the establishment of primary imprints in plants is closely linked to transposable element silencing, with transposons and other repeats serving as the sites of DNA demethylation in *Arabidopsis*, rice, and maize (Kinoshita et al. 2007; Gehring et al. 2009; Hsieh et al. 2009; Villar et al. 2009; Zemach et al. 2010a; Ibarra et al. 2012; Pignatta et al. 2014; Wang et al. 2015). The movement of transposable elements has therefore been widely proposed to generate new imprinted genes (McDonald et al. 2005; Wolff et al. 2011; Jiang and Kohler 2012; Gehring 2013; Vu et al. 2013). For example, DNA methylation of a transposable element that inserts near the transcriptional start site of a gene can lead to gene silencing, which can in turn be relieved by DME-catalyzed demethylation in the central cell to produce maternal-specific expression in the endosperm (Fig. 4A). This is apparently what happened to the *Arabidopsis* maternally expressed imprinted gene *FWA* (Fig. 3A) and many other imprinted genes (Kinoshita et al. 2007; Fujimoto et al. 2008; Gehring et al. 2009; Wolff et al. 2011). Although the creation of an imprinted gene from one that is bialleli-

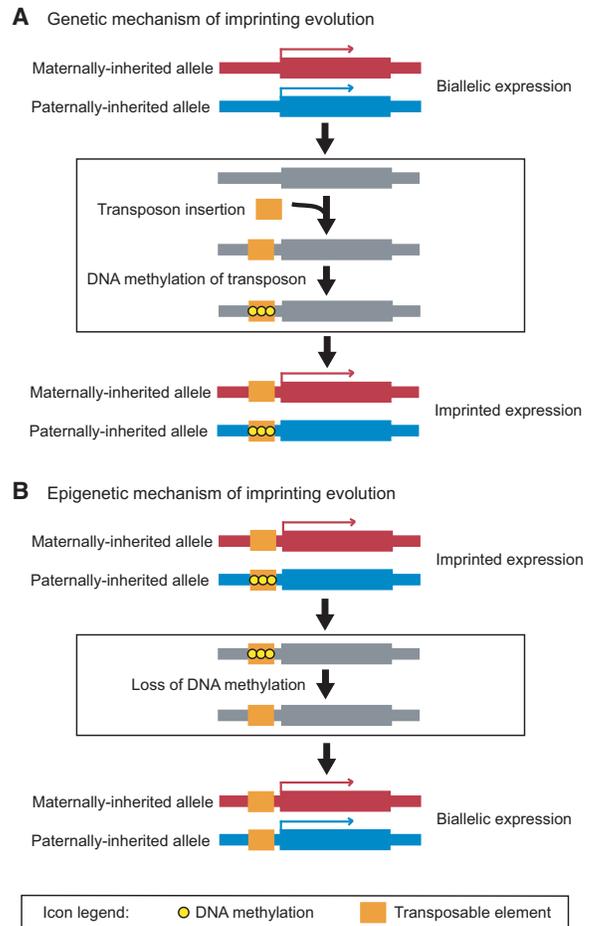


Figure 4. Evolution of imprinted gene expression through genetic mechanism via transposon insertion (A) and epigenetic mechanism via heritable loss of DNA methylation (B).

cally expressed by a transposon insertion has yet to be explicitly demonstrated, deletions of repetitive regions have been shown to result in a loss of imprinting (Walker 1998; Villar et al. 2009). Transposon insertions can also destroy imprinting, converting an imprinted gene into a biallelically expressed one, as has been demonstrated in maize (Haun et al. 2009).

The relative simplicity, at least in theory, of creating imprinted genes by transposon insertions argues that ongoing transposition events provide a substantial pool of new imprinted genes for natural selection (Waters et al. 2013). This hypothesis is supported by the observation that, although many rice genes affected by LTR retrotransposons appear to evolve into pseudogenes, some genes remain functional and show evidence of selection consistent with neofunctionalization (Jiang and Ramachandran 2013). The high activity of transposons that is characteristic of plant genomes (Huang et al. 2012) may help explain why plant imprinted genes are poorly conserved (Luo et al. 2011; Waters et al. 2011, 2013).

Although transposon insertion is a straightforward mechanism for bringing a gene under the regulatory

sway of DNA methylation, methylation patterns can diverge between individuals without an accompanying change of DNA sequence (Becker and Weigel 2012; Weigel and Colot 2012). This phenomenon is referred to as epigenetic mutation, and the alleles that bear differential methylation patterns are termed epigenetic alleles or epialleles. Plant DNA methylation patterns can diverge rather rapidly (Becker et al. 2011; Schmitz et al. 2011, 2013; Becker and Weigel 2012; Chodavarapu et al. 2012; Hagmann et al. 2015), and epialleles with major phenotypic consequences have been identified in a number of plant species (Weigel and Colot 2012; Zhang et al. 2012; Silveira et al. 2013). For example, stable unmethylated epialleles of *FWA* cause a strong delay of flowering (Soppe et al. 2000; Kankel et al. 2003). Heritable DNA methylation epialleles can therefore potentially account for some of the differences in imprinted gene expression observed within plant populations (Fig. 4B). Consistent with this possibility, differential DNA methylation has been correlated with imprinting divergence among *Arabidopsis* ecotypes (Pignatta et al. 2014). However, extensive intraspecies DNA methylation differences (Becker et al. 2011; Schmitz et al. 2011, 2013; Becker and Weigel 2012; Chodavarapu et al. 2012; Pignatta et al. 2014; Hagmann et al. 2015) and lack of characterization of the regulatory regions of the vast majority of plant imprinted genes complicate the assignment of any particular methylation polymorphism as the cause of an observed difference in imprinted expression. Thus, although epigenetic evolution of plant imprinted genes remains to be unambiguously demonstrated, this process quite likely contributes to imprinting divergence, at least on a relatively short time scale.

Evolutionary drivers and consequences of genomic imprinting

Monoallelic gene expression is generally disadvantageous in diploid organisms because deleterious mutations cannot be complemented by a functional homologous locus present in the same nucleus (Wilkins and Haig 2003). For example, mutations in the maternally expressed *ME-DEA* gene result in aborted seeds even in the presence of a functional paternally inherited copy (Grossniklaus et al. 1998; Kinoshita et al. 1999; Luo et al. 2000). The prevalence of genomic imprinting therefore suggests that imprinting is associated with fitness benefits that outweigh the costs—benefits that are likely linked to the reproductive strategies of the lineages within which imprinting occurs (Jiang and Kohler 2012; Patten et al. 2014; Pires and Grossniklaus 2014; Wolf et al. 2014).

Known instances of classical genomic imprinting are confined to therian (marsupial and eutherian) mammals and flowering plants, with imprinting likely evolving at the same time as the transient extraembryonic nutritive tissues (placenta and endosperm) characteristic of each clade (Renfree et al. 2013; Pires and Grossniklaus 2014). In mammals, the origins of both imprinting and placental development are linked to regulatory novelties resulting from LTR retrotransposon activity (Renfree et al. 2013),

while plant imprinting is mostly confined to the endosperm and is absent or short-lived in embryos, seedlings, and adult vegetative tissues (Jahnke and Scholten 2009; Zhang and Borevitz 2009; He et al. 2010; Autran et al. 2011; Hsieh et al. 2011; Luo et al. 2011; Chodavarapu et al. 2012; Nodine and Bartel 2012; Raissig et al. 2013; Del Toro-De Leon et al. 2014; Pignatta et al. 2014). Given that both the placenta and endosperm serve as the interface between the maternal parent and its dependent offspring, imprinting is inextricably shaped by processes and forces governing sexual reproduction. Numerous hypotheses attempt to explain how imprinting might be associated with increased fitness. These hypotheses are not necessarily mutually exclusive; imprinting of different genes may be shaped by different selective forces, a combination of selective forces may influence the imprinting of a particular gene, and the relative impact of selective forces may vary over the evolutionary history of a lineage.

Kinship or parental conflict hypothesis

The currently predominant theory of genomic imprinting is the kinship or parental conflict hypothesis (Haig and Westoby 1989). It predicts that, in situations where the female parent contributes resources to offspring development after fertilization and can bear the offspring of multiple males, the overall fitness of males is increased if their offspring thrive at the cost of other offspring borne by the female parent, whereas the fitness of females is increased if the female is able to have as many successful offspring as possible. This drives paternal expression of genes that promote nutrient acquisition in the offspring and maternal expression of genes that restrict nutrient allocation to any one offspring. The conflict unfolds between maternally and paternally expressed genes within the offspring (Haig 2014).

In addition to the “placental habit” forming an environment in which parental conflict is theorized to occur (Crespi and Semeniuk 2004), this hypothesis receives wide support from in-depth investigations of the functions of mammalian imprinted genes (Frost and Moore 2010; Ferguson-Smith 2011) and some support from studies in plants (Huh et al. 2008; Kohler and Weinhofer-Molisch 2010; Pires and Grossniklaus 2014). Many mammalian imprinted genes affect resource acquisition from the maternal parent either by direct regulation of nutrient transfer from the placenta and embryo growth or through influence on maternal–offspring interactions (Bartolomei and Ferguson-Smith 2011). Crosses between *Arabidopsis* plants of different ploidy that increase paternal gene dosage result in larger seeds, whereas those that increase maternal gene dosage result in smaller seeds (Scott et al. 1998). The balance between maternal and paternal alleles in interploidy crosses also influences resource allocation in maize endosperm (Li and Dickinson 2010). Perturbations to *Arabidopsis* gamete DNA methylation likewise have effects on seed size that vary depending on which parental gamete was affected and are consistent with parental conflict theory (Adams et al. 2000; Xiao et al. 2006). Additionally, imprinted genes in maize, rice, and *Arabidopsis* are

enriched for regulatory roles (Luo et al. 2011; Waters et al. 2013; Pignatta et al. 2014), with strong effects on endosperm growth resulting from loss-of-function mutations in specific genes, particularly those encoding PRC2 components (Grossniklaus et al. 1998; Kinoshita et al. 1999; Luo et al. 2000; Hermon et al. 2007). Imprinted genes also tend to show molecular signatures of the conflict between male and female fitness (Pires and Grossniklaus 2014).

However, parental conflict theory is not obviously consistent with all features of imprinting, especially in plants. First, if nutrient acquisition by the developing offspring is the main driver of imprinted expression, one might expect to observe imprinting in the growing plant embryo in addition to extraembryonic nutritive tissues, as is seen in mammals (Frost and Moore 2010; Renfree et al. 2013). Instead, imprinting in the embryo is rare and transient (Jahnke and Scholten 2009; Autran et al. 2011; Hsieh et al. 2011; Luo et al. 2011; Nodine and Bartel 2012; Rajsig et al. 2013; Del Toro-De Leon et al. 2014; Pignatta et al. 2014). It is possible that this difference between plants and mammals reflects restrictions imposed by underlying biological differences, such as two fertilization events versus one, the extent to which extraembryonic tissues regulate embryo growth, the generally much shorter developmental period that separates plant male and female gametes, and available mechanisms to differentially mark plant egg and sperm cells. Nonetheless, the preponderance of imprinting in the endosperm suggests a more intimate link with this tissue than one would predict based on parental conflict considerations.

Another incongruence is that parental conflict is predicted to drive imprinting to the complete silencing of one allele in most cases (Wilkins and Haig 2003), but many plant imprinted genes display only moderate biases (Luo et al. 2011; Waters et al. 2013). It is possible to explain this by interpreting the apparently rapid rate of imprinting evolution in plants (Luo et al. 2011; Waters et al. 2013) as an indication that many currently imprinted genes have acquired imprinting recently and/or have not yet experienced strong selection (Waters et al. 2013). Furthermore, reactivation of paternally inherited alleles that results in incomplete maternal bias may be favored under some circumstances (Wilkins and Haig 2002). The presence of imprinted expression in self-fertilizing plants, such as *Arabidopsis* and domesticated rice cultivars (Bechsgaard et al. 2004; Li et al. 2006; Londo et al. 2006), is also somewhat at odds with parental conflict theory, as the resulting monogamy would not place the related maternal and paternal genomes in conflict (Jiang and Kohler 2012). However, imprinting is plausibly inherited from recent outcrossing ancestors, and the complex webs of compensating maternally and paternally biased expression would likely take a long time to unravel (Wilkins and Haig 2003).

An additional potential challenge to the parental conflict theory arises from the recent characterization of the paternally expressed *Arabidopsis* gene *ADMETOS* (Kradolfer et al. 2013). *ADMETOS* is overexpressed in triploid *Arabidopsis* seeds created through fertilization with diploid sperm. Such seeds exhibit overexpression of other imprinted genes, including maternally biased ones. Muta-

tion of *ADMETOS* reduces the expression of several maternally expressed genes, suggesting that *ADMETOS* is a positive regulator of these genes—a function that a paternally expressed gene would not be predicted to have by parental conflict theory. However, this effect of *ADMETOS* appears to be restricted to seeds with unbalanced ploidy, in which key regulatory pathways such as PRC2 do not function properly (Kradolfer et al. 2013), so that *ADMETOS* may not promote the expression of maternally biased genes in normal diploid seeds. Furthermore, the *admetos* mutation may affect the expression of imprinted genes indirectly, and *ADMETOS* appears to promote endosperm growth by delaying cellularization (Kradolfer et al. 2013), a function consistent with parental conflict.

Perhaps the most difficult to explain in terms of parental conflict theory is the imprinted expression of the maize gene *Meg1*. *Meg1* promotes the establishment and differentiation of the endosperm nutrient transfer cells and consequently positively regulates the uptake of maternal nutrition by the developing seed (Costa et al. 2012). Increased *Meg1* dosage leads to larger embryos and endosperm. Thus, *Meg1* is precisely the type of gene predicted to be imprinted but, contrary to expectation, is maternally expressed. Similarly, overexpression of the maternally biased *Arabidopsis* imprinted gene *AtFH5* may cause overgrowth of the chalazal endosperm compartment implicated in the transfer of maternal resources (Fitz Gerald et al. 2009). Although this “wrong way” imprinting is not entirely incompatible with parental conflict (Iwasa et al. 1999; Pires and Grossniklaus 2014), maternal expression of genes that promote the transfer of maternal resources requires serious consideration of alternate hypotheses for the evolution of genomic imprinting in plants, especially since plant genomic imprinting has yet to be widely associated with nutrient regulation (Gutierrez-Marcos et al. 2012).

Coadaptation hypothesis

The coadaptation hypothesis for the evolution of genomic imprinting (Wolf and Hager 2006) was inspired by adaptive correlations between the traits of mothers and offspring in several lineages (Kolliker et al. 2000; Agrawal et al. 2001; Hager and Johnstone 2003; Lock et al. 2004) and the observation that increased investment of maternal resources does not necessarily increase fitness (Thomas et al. 2004; Dunger et al. 2007). For example, human babies with intermediate birth weight have the highest fitness (Ulizzi et al. 1981), which may favor coevolution of maternal and offspring traits that lead to birth weight optimization (Wolf and Brodie 1998). Theoretical work supporting the coadaptation hypothesis shows that selective pressure for closer integration between coadapted maternal and offspring traits can drive the evolution of maternally biased gene expression (Wolf and Hager 2006).

The coadaptation hypothesis has several limitations. It assumes that similarity between the alleles expressed in mothers and offspring will be favored and therefore can only explain the evolution of maternally expressed imprinted genes, at least in the context of plant reproduction.

Because the coadaptation hypothesis relies on allele similarity rather than dosage sensitivity, substantial heterozygosity within a population is required for the selection of imprinted expression; maternally biased expression offers no benefit if the maternal and paternal alleles are identical (Haig 2014). Furthermore, no imprinted gene has yet been shown to function along the lines predicted by the coadaptation hypothesis (Haig 2014). Despite these limitations, the coadaptation hypothesis may explain the imprinting of some genes through the benefits of closer cooperation between mothers and offspring rather than conflict between maternally and paternally inherited genes within the offspring.

Coadaptation may have plausibly favored the evolution of imprinting at genes that encode components of the plant PRC2 complex. Two of the *Arabidopsis* genes encoding PRC2 components are imprinted and maternally expressed (Grossniklaus et al. 1998; Kinoshita et al. 1999; Luo et al. 2000; Jullien et al. 2006b), placing the complex that silences the maternal alleles of most, if not all, paternally expressed genes (Hsieh et al. 2011; Wolff et al. 2011; Makarevitch et al. 2013; Zhang et al. 2014) under maternal control. PRC2 component genes are also maternally expressed in rice and maize endosperm, but these genes either encode PRC2 components that are different from the ones imprinted in *Arabidopsis* or evolved imprinting independently (Danilevskaya et al. 2003; Spillane et al. 2007; Luo et al. 2009; Pires and Grossniklaus 2014). The convergent evolution of PRC2 imprinting indicates that maternal expression of PRC2 is generally favored in flowering plants. PRC2 preferentially controls transcription factors that are master regulators of development and has thousands of targets in the endosperm (Weinhofer et al. 2010; Makarevitch et al. 2013; Zhang et al. 2014; Kohler and Lafon-Placette 2015; Pu and Sung 2015). Imprinting of such a multifaceted complex is perhaps more likely explained through the integration of female and offspring traits than by restriction of nutrient allocation to the offspring, as would be predicted by parental conflict. Importantly, the imprinting of PRC2-regulated paternally expressed genes is not expected to be driven by coadaptation. Therefore, somewhat counterintuitively, imprinting of PRC2 genes and the imprinted genes controlled by PRC2 may be guided by distinct evolutionary forces.

Dosage hypothesis

As mentioned above, an implication of the parental conflict hypothesis is that the functions of imprinted genes are dose-dependent; otherwise, monoallelic expression would carry no benefit. With this in mind, the “dosage hypothesis” (Dilkes and Comai 2004) was developed as a more general explanation for the evolution of imprinted expression. This hypothesis proposes that reduced expression from one allele will be favored by natural selection if it results in a more optimal abundance of the gene product. The gene does not need to be involved in resource allocation or indeed any particular pathway, although genes near the top of regulatory hierarchies and those that encode subunits of multiprotein complexes may be affected more

frequently (Birchler et al. 2001). Because optimal gene dosage is not necessarily achieved by the complete silencing of one allele, the dosage hypothesis allows for incomplete parental bias as a stable evolutionary state. These features of the hypothesis fit the observed diversity of plant imprinted genes, the prevalence of imprinted genes with regulatory functions, and the tendency for partial rather than complete parental bias (Gehring et al. 2011; Hsieh et al. 2011; Luo et al. 2011; Waters et al. 2011, 2013; Wolff et al. 2011; Zhang et al. 2011; Pignatta et al. 2014). However, the dosage hypothesis does not obviously account for the concentration of imprinted expression in endosperm.

Imprinting under relaxed selection

So far, we have discussed several hypotheses under which genomic imprinting is favored by natural selection. However, it is quite possible that the imprinted expression of many plant genes arose under weak, if any, selection. The imprinting status of plant genes appears to evolve quite rapidly; there is substantial intraspecific imprinting variation (Waters et al. 2013; Pignatta et al. 2014) and almost no overlap between the imprinted genes of *Arabidopsis*, rice, and maize (Luo et al. 2011; Waters et al. 2011, 2013). Most of the examined *Arabidopsis* imprinted genes were subjected to recent gene duplication events, have increased rates of amino acid changes, and appear to have acquired expression specificity to flowers or seeds compared with their more broadly expressed nonimprinted homologs (Wolff et al. 2011; Qiu et al. 2014). Inactivating mutations of many imprinted genes have no apparent influence on seed development (Berger et al. 2012; Wolff et al. 2015). This is consistent with imprinted genes undergoing neofunctionalization following gene duplication (Spillane et al. 2007; Bai and Settles 2014), whereas the low intraspecies and interspecies rates of conservation imply frequent loss of imprinting during evolution. Imprinting may thus be a transient state that facilitates neofunctionalization by reducing selection against mutations of silent alleles while accelerating selection of expressed alleles, in essence rendering imprinting as a form of diversifying selection (Beaudet and Jiang 2002; Bai and Settles 2014).

One can envision how this might work by considering the *FWA* gene. *FWA* is DNA methylated and silenced in most tissues and is specifically activated in the central cell by DME-mediated demethylation, resulting in maternal-specific expression in the endosperm (Fig. 3A; Kinoshita et al. 2004). Loss of *FWA* methylation leads to ectopic expression and strongly delayed transition to reproductive growth and flowering (Soppe et al. 2000; Kinoshita et al. 2004, 2007), whereas inactivating *fwa* mutations do not have an obvious phenotype (Soppe et al. 2000). If *FWA* were expressed throughout the plant and if delayed flowering were deleterious under a given set of environmental conditions, then mutations that inactivate *FWA* would be favored. DNA methylation of *FWA* accomplishes the same end while preserving gene expression in the seed and providing an opportunity for evolution of a new function. In this view, the imprinting of most genes in the seed

has no fitness benefit except perhaps via the silencing of these genes in other tissues (Berger et al. 2012), with imprinted genes generally either degenerating into pseudogenes or acquiring new functions and biallelic expression. The lack of imprinted gene conservation implies that long-term persistence of neofunctionalized plant imprinted genes is rare.

Because the two main mechanisms known to be responsible for plant imprinting—DME-catalyzed DNA demethylation and PRC2-catalyzed histone methylation—have functions unrelated to imprinting, selection on imprinted genes is unnecessary to explain the maintenance of imprinting mechanisms. In fact, the activity of DME in the male vegetative cell (Fig. 2), where it demethylates some of the same genes that are imprinted in the endosperm (Schoft et al. 2011; Ibarra et al. 2012), may be a hint about the evolutionary origins of imprinting in flowering plants. Gymnosperms such as conifers have no endosperm, the function of which is performed by the

haploid female gametophyte (Fig. 5; Baroux et al. 2002). How the endosperm evolved in flowering plants remains a mystery, but a leading hypothesis postulates that the female gametophyte became sexualized (Nowack et al. 2007). If DME-type activity in the female gametophyte—for example, in the ventral canal cell that undergoes fertilization in some gymnosperms (Friedman and Floyd 2001)—predates the evolution of the endosperm, imprinting and the endosperm may have arisen simultaneously upon the evolution of double fertilization in the ancestor of flowering plants (Fig. 5). This would explain the predominance of imprinted expression in the endosperm without recourse to the argument that imprinting in the endosperm is especially favored by natural selection.

Imprinting as a post-zygotic barrier to hybridization

As discussed above, imprinting may have important consequences for plant evolution by promoting genetic

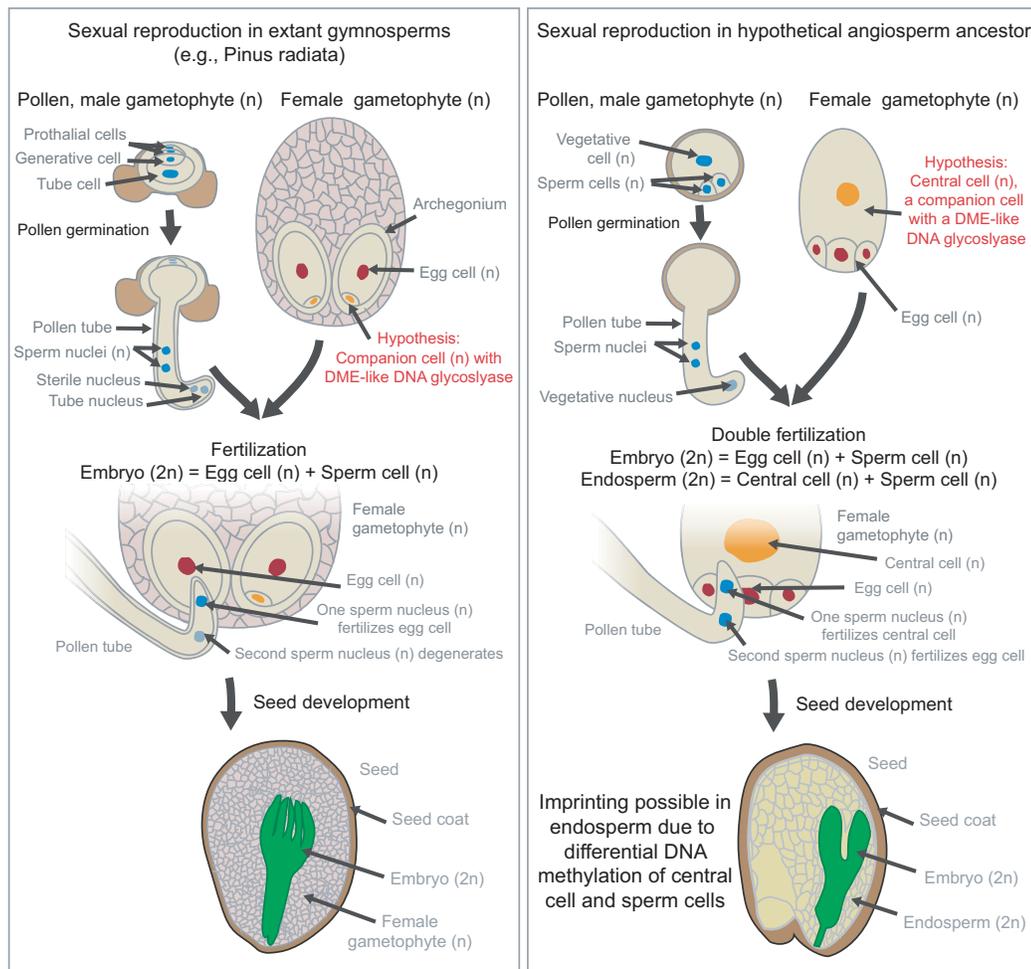


Figure 5. Model for the simultaneous evolution of imprinting and endosperm in the ancestor of angiosperms (flowering plants). Angiosperms emerged from a gymnosperm (nonflowering seed plant) lineage, evolving flowers, fruits, and endosperm. Endosperm potentially evolved through the sexualization of a female gamete companion cell, such as the ventral canal cell (Friedman and Floyd 2001; Rudall 2006), via fusion with one of the two sperm cells of pollen. Activity of a DME-like enzyme in the sexualized female gamete companion cell would give rise to an endosperm with DNA methylation-based imprints in the ancestor of modern angiosperms.

neofunctionalization. Another proposed evolutionary consequence of imprinting is the facilitation of speciation following polyploidization (Schatlowski and Kohler 2012). Crosses between polyploid plants and their diploid relatives alter the usual balance between maternal and paternal chromosomes. If dosage-sensitive genes are expressed differently from maternal and paternal alleles, either maternal or paternal excess can reduce offspring fitness. Therefore, genomic imprinting may pose a reproductive barrier between plants of different ploidy, leading to reproductive isolation and speciation (Haig and Westoby 1991). This hypothesis is supported by the long-standing observation that interploidy crosses tend to fail due to aberrant endosperm development (Kohler and Kradolfer 2011; Schatlowski and Kohler 2012; Birchler 2014). More direct evidence was provided by the demonstration that mutation of the paternally expressed *Arabidopsis* imprinted gene *ADMETOS* rescues seed abortion caused by excess paternal ploidy (Kradolfer et al. 2013). The finding that the dosage of a single imprinted gene is crucial for the success of triploid seeds may indicate that the majority of imprinted genes is not involved in interploidy interactions. However, because mutation of *ADMETOS* normalizes the expression of many imprinted genes in triploid endosperm, it is quite possible that *ADMETOS* has such a powerful effect through the regulation of imprinted genes in general (Kradolfer et al. 2013). This conclusion is supported by the recent finding that mutations in three other paternally expressed *Arabidopsis* genes rescue triploid seeds, with one of these, *svvh7*, also normalizing the expression of other imprinted genes (Wolff et al. 2015).

Concluding remarks

Five years ago, about a dozen imprinted genes had been identified in plants, with handfuls detected in any one species (Berger and Chaudhury 2009). Maternal-specific DNA demethylation and histone methylation by PRC2 were known to control the differential activation and silencing of maternal and paternal alleles of some of these genes, but whether these regulatory paradigms were reflective of the bulk of plant imprinting was unclear (Huh et al. 2008). Since then, hundreds of new imprinted genes have been discovered, and the generality of the mechanisms of imprinted gene regulation has been firmly established (Gehring et al. 2011; Hsieh et al. 2011; Luo et al. 2011; Waters et al. 2011, 2013; Wolff et al. 2011; Zhang et al. 2011, 2014; Ibarra et al. 2012; Rodrigues et al. 2013; Du et al. 2014; Pignatta et al. 2014; Xu et al. 2014). Many mechanistic mysteries remain, including the existence of primary imprints other than DNA methylation, the plasticity of epigenetic marks during early seed development, the biogenesis and functions of imprinted sRNAs in endosperm, and the targeting specificity of DME-like enzymes. Nevertheless, the current understanding of the core mechanisms responsible for plant imprinting appears to be fairly robust. In contrast, our understanding of the evolution and biological significance of plant imprinting is in its infancy. Very few plant imprinted genes have known functions, which

is perhaps to be expected given the recent order of magnitude expansion in the number of identified imprinted genes. Furthermore, none of the proposed theories for the natural selection of imprinted gene expression are fully consistent with all of the evidence. Imprinting of some genes, such as those encoding PRC2 components, is clearly very important, yet we must consider the sobering possibility that the imprinting of most plant genes is of little or no fitness benefit. Given this state of affairs, elucidation of the biological functions of plant imprinted genes should be a priority.

Acknowledgments

We thank Robert Fischer for comments on the manuscript, and Anna Koltunow and Brian Dilkes for helpful discussions. This work was supported by National Institutes of Health grant GM069415 and National Science Foundation grant IOS-1025890 to D.Z.

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Genes Dev. 2015, **29**:

Access the most recent version at doi:[10.1101/gad.269902.115](https://doi.org/10.1101/gad.269902.115)

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