Natural Pathways to Polyploidy in Plants and Consequences for Genome Reorganization

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Chromosome pairing · Dobzhansky-Muller incompatibility · Hybrid dysregulation · Genome evolution · Genome merging · Genome restructuring · Speciation · Transposable elements · Unreduced gametes · Whole genome doubling

Abstract
The last decade highlighted polyploidy as a rampant evolutionary process that triggers drastic genome reorganization, but much remains to be understood about their causes and consequences in both autopolyploids and allopolyploids. Here, we provide an overview of the current knowledge on the pathways leading to different types of polyploids and patterns of polyploidy-induced genome restructuring and functional changes in plants. Available evidence leads to a tentative ‘diverge, merge and diverge’ model supporting polyploid speciation and stressing patterns of divergence between diploid progenitors as a suitable predictor of polyploid genome reorganization. The merging of genomes at the origin of a polyploid lineage may indeed reveal different kinds of incompatibilities (chromosomal, genic and transposable elements) that have accumulated in diverging progenitors and reduce the fitness of nascent polyploids. Accordingly, successful polyploids have to overcome these incompatibilities through non-Mendelian mechanisms, fostering polyploid genome reorganization in association with the establishment of new lineages. See also sister article focusing on animals by Collares-Pereira et al., in this themed issue.

Polyploidy (i.e. the merging of more or less divergent genomes associated with whole genome duplication) is an important factor in eukaryote evolution [Lynch, 2007; Otto, 2007]. For instance, it is now clear that all flowering plants have gone through at least one round of polyploidy [Jiao et al., 2011]. Polyploidy long remained a favored topic of evolutionary studies in plants [Muntzing, 1936; Clausen et al., 1945; Stebbins, 1971; Grant, 1981; Levin, 2002; Comai, 2005; Doyle et al., 2008; Leitch and Leitch, 2008; Parisod et al., 2010a; Soltis and Soltis, 2012], although several animal taxa are known to contain polyploid forms [Otto and Whitton, 2000; Mable et al., 2011]. Cross-talk between these traditional fields as promoted by this issue is expected to foster advances in our understanding of the potential advantages and disadvantages of being polyploid.
The last decade has shown a renewed interest in examining and integrating the consequences of polyploidy in different organisms to shed light on this rampant evolutionary process. Here, we provide an overview of the current knowledge on the origins of polyploids and their consequences for genome organization in plants. We will first describe the different types of polyploids and the pathways leading to their formation. Then, we will expand on observed patterns of polyploidy-induced genome changes and explore their possible causes and consequences for the establishment of new polyploid lineages. As a whole, we highlight evidence supporting the emergence of a model stressing divergence between diploid progenitors as a suitable predictor of genome reorganization after polyploidization. The merging of genomes at the origin of polyploid lineages indeed reveals different kinds of incompatibilities that have accumulated during progenitor divergence and that reduce the fitness of nascent polyploids. Accordingly, successful polyploids have to overcome these incompatibilities through non-Mendelian mechanisms, fostering specific genome changes going along with their establishment.

Fig. 1. Natural pathways to polyploidy. The origin of both autotetraploids and allotetraploids involve the merging of more or less divergent diploid genomes through the formation of diploid (i.e. homoploid bridge), triploid (i.e. unilateral pathway) or tetraploid (i.e. bilateral pathway) hybrids. Spontaneous somatic chromosome doubling is assumed to be rare (dashed arrows). Recently formed neopolyploids go through a phase of intense genome reorganization (figured by changing colors) referred to as diploidization and leading to the evolution of paleopolyploids.

Paleo- versus Neopolyploids and Auto- versus Allopolyploids

Polyploidy may be a confusing term because of both changing terminologies and recent paradigm shifts. In particular, the last decade unraveled the considerable genetic redundancy presented by plant genomes and highlighted the highly dynamic nature of polyploid genomes [Soltis and Soltis, 2012]. Genome reorganization, involving drastic restructuring and functional alterations in association with polyploidy, is commonly referred to as diploidization and generally restores a secondary diploid-like behavior of polyploid genomes. Accordingly, a temporal distinction between paleopolyploids (i.e. ancient polyploids with diploidized genomes) and neopolyploids (i.e. young polyploids without diploidized genomes) seems useful [Blanc and Wolfe, 2004]. This review is mainly focused on neopolyploids, including both experimental (i.e. synthetic) and naturally formed (i.e. nascent or established) polyploids. Nascent, established and paleo-polyploids hardly represent clear-cut categories, but may highlight stages in the evolution of polyploid lineages likely driven by contrasting processes.

The classification of neopolyploids into 2 main categories (fig. 1) based on their origin is still controversial [Clausen et al., 1945; Ramsey and Schemske, 1998]. Autopolyploids are generally considered to have arisen within or among populations of a single species by the doubling of structurally similar, homologous chromosome sets (AAAA), whereas allopolyploids typically involve interspecific hybridization associated with the doubling of non-homologous (i.e. homeologous) chromosome sets (AABB). To account for natural hybrid polyploids forming multivalents, Stebbins [1947] defined ‘inter-racial autopolyploids’ or ‘segmental allopolyploids’ to denote the doubling of partially differentiated genomes (AAA’A’). It is now widely accepted that polyploidy encompasses a continuum from the doubling of identical genomes to the doubling of highly differentiated genomes (fig. 1). Accordingly, all natural polyploids likely consist of more or less divergent genomes having been merged at their origin.

The most obvious characteristic which may distinguish types of polyploids is the pairing behavior of the chromosomes in meiosis [Jackson, 1982]. Autopolyploids have multiple homologous chromosomes and thus mainly form multivalents, while allopolyploids form predominantly bivalents as homologous chromosomes do not regularly pair [Ramsey and Schemske, 2002]. Chromosome pairing is, however, affected by sev-
eral factors and predominant bivalent pairing in autopolyploids or multivalent pairing in polyploids of hybrid origin is reported [Jenczewski and Alix, 2004; Otto, 2007]. Patterns of chromosome pairing may thus be a misleading criterion to classify polyploids. Accordingly, a classification of polyploid based on patterns of segregation should be preferred [Soltis et al., 2007; Parisod et al., 2010a]. Autopolyploids indeed present 4 homologous chromosomes that can randomly pair at meiosis, even if strictly forming bivalents, resulting in random segregation of chromosomes or chromatids and leading to poly-
somic inheritance with possible double reduction [Jack-
son and Jackson, 1996; Hauber et al., 1999; Landergott et
al., 2006; Stift et al., 2008]. This results in the production of homozygotes and different types of partial heterozy-
gotes (AAAa, AAaa, Aaaa for a tetraploid locus with 2 alleles [Bever and Felber, 1992; Ronfort et al., 1998;
Butruille and Boiteux, 2000; Luo et al., 2006]). Polysomic
inheritance occurs even if homologous chromosomes
regularly pair as bivalents and thus is the key criterion
distinguishing auto- from allopolyploid taxa [Soltis et al.,
2007; Parisod et al., 2010a]. Noticeably, polysomic in-
heritance may represent a transient segregation pattern
in neoautopolyploids and evolve toward disomic inheri-
tance with ongoing diploidization. Accordingly, the dis-
tinction between auto- and allopolyploids would be
blurred in paleopolyploids.

Natural Pathways at the Origins of Polyploids

Somatic Doubling versus Merging of Unreduced
Gametes

Several pathways involving the spontaneous doubling of chromosome sets in somatic cells and the reunion of unreduced gametes support the formation of new poly-
ploid lineages in plants (fig. 1). Such different pathways do not seem to be equally frequent in nature [reviewed in
the meta-analysis of Ramsey and Schemske, 1998].

Mitotic nondisjunction supporting spontaneous dou-
bbling of chromosomes can occur throughout the life cycle
of a plant and may result in mixoploid organisms poten-
tially at the origin of polyploid meristematic cells that ul-
timately lead to a new polyploid organism (e.g. Primula
kewensis [Grant, 1981]). Little is known about the fre-
cuency of spontaneous chromosome doubling, parti-
cularly after events such as interspecific hybridization or
stress conditions [Lewis, 1980; Ramsey and Schemske,
1998]. Somatic doubling is commonly performed to pro-
duce synthetic polyploids supposed to mimic established
ones but is estimated to be a relatively minor pathway to
polyplod in natural populations.

Unreduced gametes (i.e. diplogametes) are produced at a much higher rate than previously assumed and may be involved in the major pathways leading to polyploidy
[Bretagnolle and Thompson, 1995; Otto and Whitton,
2000]. Several mechanisms resulting in the production of unreduced gametes have been identified in a variety of
plant taxa [reviewed in Bretagnolle and Thompson, 1995;
Brownfield and Köhler, 2011]. The production of diplo-
 gametes is highly variable among and within species, and
has been estimated at 0.56% in non-hybrid flowering
plants [Ramsey and Schemske, 1998]. Diplogametes seem
to be more frequent under environmental stresses, such
as frost, wounding, herbivory, water or nutrient shortage
e.g. Mason et al., 2011]. Noticeably, hybrids between diver-
gent genomes present up to a 50-fold increase in the
production of unreduced gamete as compared to non-
hybrid systems [e.g. Zhang et al., 2010]. In addition, the
production of diplogametes appears to be heritable and
governed by a few genes [d’Erfurth et al., 2008; Zhang
et al., 2010]. However, the molecular basis underlying the
formation of unreduced gamete begins to be unraveled,
but much remains to be understood [Brownfield and
Köhler, 2011].

Given their high rate of production, the union of un-
reduced gametes likely supports the origin of both auto-
and allopolyploids under natural conditions (fig. 1). Such
events seem frequently enough to form polyploid at an
estimated rate (10^-5 for autotetraploids and 10^-4 for allo-
tetraploids) comparable with the one of genic mutations
[Ramsey and Schemske, 1998]. Recent work having esti-
imated the rate of polyploid formation in natural popula-
tions matched these expectations [Ramsey, 2007], but addi-
tional empirical studies assessing the frequency of the
different pathways to polyploidy are needed.

Unreduced Gametes: Unilateral versus Bilateral
Polyplodization

Given the low probability of uniting 2 unreduced gam-
etes in a single step (i.e. bilateral polyploidization), the
formation of tetraploids has early been anticipated as
being mostly indirect, involving triploid intermediates
(triploid bridge supporting unilateral polyploidization; fig.
1) [Harlan and DeWet, 1975]. Triploid individuals are
indeed observed at low frequency in natural popula-
tions and easily obtained experimentally [Ramsey
and Schemske, 1998]. The fusion of a reduced with an unre-
duced gamete is expected to produce triploids that can in
turn generate tetraploids through selfing or crossing with
other triploids or diploid progenitors. The establishment of tetraploids would thus critically depend on (i) the rate of triploid formation, (ii) the fitness of triploids and (iii) the ploidy level of the functional gametes produced by triploids [Husband, 2004].

Triploidy has long been considered detrimental as triploid seeds may early abort (i.e. triploid block) [Brink and Cooper, 1947]. The endosperm (i.e. the tissue, made of one paternal and 2 maternal genomes, surrounding and providing nutrients to the embryo) indeed seems sensitive to dosage of parental genes and may fail to properly develop in polyploids with misbalanced chromosome sets. Such emphasis on the endosperm is consistent with the reduced triploid block observed in species presenting a reduced endosperm [Ramsey and Schemske, 1998; Husband, 2004]. Successive models based on the relative ploidy of seed tissues have been developed to account for triploid seed production despite triploid block [Muntzing, 1930; Johnston et al., 1980; Lin, 1984]. Köhler et al., [2010] recently pointed out that failure of endosperm development in both homoploid and interploid hybrids might be associated with differently imprinted genes of the Polycomb group. Accordingly, parental divergence and/or ratios of paternal versus maternal dosage would result in unbalanced interactions between global transcriptional repressors of the Polycomb group and their targets (i.e. homeotic genes and downstream genes as well as transposable elements), leading to a crash of the endosperm in triploids. Uncertainties about links between these mechanisms and expected incompatibilities reducing fitness remain. However, viable triploids present unexpected fertility. A mean pollen fertility of 31.9% has indeed been reported in triploid Angiosperms by Ramsey and Schemske [1998]. Triploids indeed produce a relatively large amount of viable, euploid gametes (n = x, 2x, 3x), regardless of their auto- or allopolyploid origin and may thus strongly impact on the formation of polyploids [Husband, 2004]. However, additional insights on the influence of triploid intermediates on the origin of polyploids in natural populations, particularly in primary contact zones between diploids and tetraploids, would be valuable.

Tetraploids can be formed without triploid intermediates through either homoploid hybrids (i.e. homoploid bridge) or the direct union of 2 diplogametes (i.e. bilateral polyploidization; fig. 1). Hybrids seem to present an increased production of diplogametes as shown by the average 27% reported in hybrid systems as compared to 5.6% in non-hybrid systems [Ramsey and Schemske, 1998]. Accordingly, homoploid hybrids could be expected to sustain polyploidization [Rieseberg and Willis, 2007]. Hybrids can also be directly polyploid when formed through bilateral polyploidization. This pathway has been reported at the origin of both auto- and allotetraploid taxa [Ramsey and Schemske, 1998; Husband, 2004]. Plants producing particularly high levels of diplogametes may indeed foster bilateral polyploidization, especially in the case of self-fertilizing individuals [Bretagnolle and Thompson, 1995; Bretagnolle, 2001].

Based on extensive data [analyzed in Ramsey and Schemske, 1998], bilateral polyploidization is estimated to produce polyploids at a rate almost similar to unilateral polyploidization. However, the frequency of spontaneous somatic doubling at the origin of natural auto- and allopolyploids should be further empirically estimated. Accordingly, the concluding remark of Ramsey and Schemske [1998] that ‘comprehensive examination of the pathways, mechanisms and rate of polyploid formation in natural populations’ remains largely appropriate.

Multiple Origins and Multiple Pathways Produce Variable Polyploids

Polyploidy has long been considered exceptional with polyploid species typically being monophyletic and genetically depauperate [Ehrendorfer, 1980; Favarger, 1984]. Multiple origin of polyploid species is now considered the rule rather than the exception [Soltis and Soltis, 1999]. It has been demonstrated for several allopolyploids [Wendel and Cronn, 2003; Abbott and Lowe, 2004; Soltis et al., 2004; Arrigo et al., 2010] and autopolyploids [Shore, 1991; Segraves et al., 1999; Soltis and Soltis, 1999; Parisod and Besnard, 2007], despite notable exceptions such as Arabidopsis succica [Jakobsson et al., 2006] or Draba ladiina [Widmer and Baltisberger, 1999]. Noticeably, multiple origins may occur over restricted geographical distributions and/or short evolutionary timescales as illustrated by the allopolyploid Tragopogon miscellus that formed at least 21 times independently during the last 50–60 years [Soltis et al., 2012].

Multiple origins of polyploids may involve genetically and morphologically differentiated parents, and may result in considerable genetic and phenotypic variability as well as variable nuclear or nucleo-cytoplasmic interactions at the polyploid level [Soltis and Soltis, 1999; Wendel, 2000; Mable, 2003]. Adding to such complexity, independent polyploid lineages may have originated through varied pathways, multiplying interactions among genomes. Although likely, this hypothesis has apparently not been tested yet. Finally, independently formed polyploid lineages may further hybridize [e.g. Modliszewski

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and Willis, 2012]. Accordingly, the evolutionary history of a given polyploid taxon may be much more complex than usually assumed and hardly disentangled. In particular, the multifarious origin of current lineages, together with genome reorganization (see below), certainly participates in the evolution of highly variable polyploid gene pools.

**Patterns of Genome Changes after Polyploidization**

The last decade revealed that polyploidization triggers genome changes highlighted as departure from the predicted additivity of parental genomes in polyploids. Thus, polyploidy has been compared to a genome shock inducing drastic genome reorganization [reviewed in Comai, 2005; Doyle et al., 2008; Leitch and Leitch, 2008]. Genome changes have early been categorized based on their genetic or epigenetic nature and their impact on either structural or functional genomic traits (fig. 2; table 1). The timing of such genome reorganization further distinguishes short-term revolutionary changes observed in the first few generations following polyploidization and the long-term evolutionary changes taking place during the lifespan of the polyploid lineage [Feldman et al., 2012].

**Genome Restructuring following Polyploidization**

Genome restructuring events including DNA sequence loss, amplification or reduction of repetitive sequences, or large chromosome repatterning involving deletion, insertion, inversion, translocation of chromosomal segments has been reported following polyploidy in several systems (see table 1 for references). Despite drastic restructuring reported in both the short- and the long-term in several polyploids (see Brassica, Nicotiana, Tragopogon or Triticum), a couple of counter examples revealed limited structural changes (see Gossypium or Spartina). Rapid loss of DNA sequences is common after polyploidy and genome downsizing seems to be a general response to both auto- and allopolyploidy [Leitch and Bennett, 2004; Eilam et al., 2010; Yang et al., 2011]. Nevertheless, some studies reported no DNA loss [Ozkan et al., 2006; Mestiri et al., 2010; Zhao et al., 2011] or genome expansion [Leitch et al., 2008]. Large genome rearrangements such as inversion, translocation, deletion or aneuploidy have been reported in autoploids (see Arabidopsis or Goldbachia) and allopolyploids (see Brassica, Nicotiana or Tragopogon). Several studies highlighted a biased restructuring towards either the paternal (e.g. Nicotiana) or the maternal (e.g. Spartina) subgenomes.

**Functional Changes following Polyploidization**

Numerous studies highlighted changes in epigenetic patterning and gene expression in both synthetic and established polyploids (see table 1 for references). Reports from both synthetic and established polyploids indicate that functional changes occur quickly and are reproducible to a large extent (e.g. Brassica, Tragopogon or Triticum). Noticeably, methylation changes and expression of the alleles originating from one of the parental genome (i.e. expression bias) or changing expression towards the levels of one of the parental (i.e. expression dominance) is commonly reported [Grover et al., 2012; Soltis et al., 2012; Wendel et al., 2012]. However, limited changes in methylation patterns and gene expression have been reported in specific allopolyploids as well [e.g. Mestiri et al.,
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<td>Del</td>
<td>Epi</td>
<td>Loss of DNA and cDNA fragments and methylation changes in synthetic accessions (F2–F5)</td>
<td>Song et al., 1995</td>
</tr>
<tr>
<td>Brassica napus</td>
<td>Allo</td>
<td>S</td>
<td>Chrom</td>
<td></td>
<td>Translocations and aneuploidy (24.1–71.4%) in synthetic accessions</td>
<td>Pires et al., 2004; Xiong et al., 2011</td>
</tr>
<tr>
<td>Brassica napus</td>
<td>Allo</td>
<td>S</td>
<td>Del</td>
<td></td>
<td>Genetic changes in 1.2% of the loci (fragment loss: 0.1–0.8%) in synthetic accessions after hybridization and/or genome doubling</td>
<td>Lukens et al., 2006; Xu et al., 2012b</td>
</tr>
<tr>
<td>Brassica napus</td>
<td>Allo</td>
<td>S</td>
<td>Epi</td>
<td></td>
<td>Alternative splicing in duplicated genes (26–30%) in synthetic and established accessions</td>
<td>Zhou et al., 2011</td>
</tr>
<tr>
<td>Brassica napus</td>
<td>Allo</td>
<td>S/L</td>
<td>Gene</td>
<td></td>
<td>Gene expression changes (38%) in synthetic and established accessions</td>
<td>Pires et al., 2004; Albertin et al., 2007; Higgins et al., 2012</td>
</tr>
<tr>
<td>Brassica napus</td>
<td>Allo</td>
<td>S</td>
<td>Chrom</td>
<td></td>
<td>Sequence repeat and chromosomal rearrangements as well as activation of retrotransposon after hybridization</td>
<td>Zou et al., 2011</td>
</tr>
<tr>
<td>Brassica napus</td>
<td>Allo</td>
<td>S</td>
<td>Del</td>
<td>Epi</td>
<td>Nonrandom fragment loss (3.5%, mostly in S5) and methylation changes (mostly in S0) in synthetic accessions</td>
<td>Gaeta et al., 2007</td>
</tr>
<tr>
<td>Brassica rapa × B. carinata</td>
<td>Allo</td>
<td>S</td>
<td>Gene, Epi</td>
<td></td>
<td>Asymmetrical genetic changes (1.8%), DNA methylation (8.8%) and gene expression (5.1%) changes detected in synthetic F1 and/or allohexaploids. Sometimes reversed by genome doubling</td>
<td>Xu et al., 2012a</td>
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<tr>
<td>Species</td>
<td>Auto/Allo</td>
<td>Timing</td>
<td>Structure</td>
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<tr>
<td>Brassica spp.</td>
<td>Allo</td>
<td>L</td>
<td>Del</td>
<td></td>
<td>Genome downsizing in natural accessions of B. napus (8%), B. juncea (8%) and B. carinata (3%)</td>
<td>Johnston et al., 2005</td>
</tr>
<tr>
<td>Gossypium hirsutum</td>
<td>Allo</td>
<td>S/L</td>
<td></td>
<td>Gene</td>
<td>Gene silencing and subfunctionalization in synthetic and established accessions</td>
<td>Adams et al., 2003</td>
</tr>
<tr>
<td>Gossypium hirsutum</td>
<td>Allo</td>
<td>L</td>
<td>Del</td>
<td></td>
<td>Conserved colinearity, but high genome turnover due to small-scale deletions in the repetitive genome fraction as well as limited transposition</td>
<td>Grover et al., 2008; Hu et al., 2010</td>
</tr>
<tr>
<td>Hordeum murinum subsp. leporinum</td>
<td>Allo</td>
<td>L</td>
<td>Del</td>
<td></td>
<td>Genome downsizing (18%) in established accessions</td>
<td>Eilam et al., 2009</td>
</tr>
<tr>
<td>Nicotiana spp.</td>
<td>Allo</td>
<td>L</td>
<td>Del, Ampl</td>
<td></td>
<td>Genome size changes in established accessions (reduction in N. tabacum, N. rustica, N. arenstii, N. rustica about 1.9–14.3% and amplification in N. clevelandii, N. quadrivalis, N. repanda, N. nesophila, N. stocktonii about 2.5–28.6%)</td>
<td>Leitch et al., 2008</td>
</tr>
<tr>
<td>Nicotiana spp.</td>
<td>Allo</td>
<td>S/L</td>
<td>Del, Ampl</td>
<td></td>
<td>Complete genome turnover despite conserved karyotype in less than 5 million years; proliferation and deletion of transposable elements</td>
<td>Lim et al., 2007; Petit et al., 2010; Parisod et al., 2012</td>
</tr>
<tr>
<td>Nicotiana tabacum</td>
<td>Allo</td>
<td>S/L</td>
<td>Chrom</td>
<td></td>
<td>Up to 3 translocations in synthetic allopolyploids and intergenomic recombination in established accessions; similar translocation in all established and 2/3 of synthetic accessions</td>
<td>Lim et al., 2004; Skalicčák et al., 2005; Koukalova et al., 2010</td>
</tr>
<tr>
<td>Nicotiana tabacum</td>
<td>Allo</td>
<td>S/L</td>
<td>Del, Ampl</td>
<td></td>
<td>Loss of repeat sequences (18%) and retrotransposon fragments (29–62.5%) mostly from the paternal genome as well as new insertions in synthetic (54) and established accessions</td>
<td>Petit et al., 2007, 2010; Renny-Byfield et al., 2011</td>
</tr>
<tr>
<td>Nicotiana tabacum</td>
<td>Allo</td>
<td>L</td>
<td>NS</td>
<td></td>
<td>Neither uniparental epigenetic silencing nor methylation changes in repeated sequences of established accessions</td>
<td>Fulneček et al., 2009</td>
</tr>
<tr>
<td>Nicotiana, arenstii, N. rustica</td>
<td>Allo</td>
<td>L</td>
<td>Chrom</td>
<td></td>
<td>Limited genetic changes in subtelomeric tandem repeats in established accessions</td>
<td>Lim et al., 2004</td>
</tr>
<tr>
<td>Senecio cambrensis</td>
<td>Allo</td>
<td>S/L</td>
<td></td>
<td>Gene</td>
<td>Reorganization of gene expression networks in synthetic and established accessions; expression restored towards parental states after genome doubling</td>
<td>Hegarty et al., 2006</td>
</tr>
<tr>
<td>Spartina anglica</td>
<td>Allo</td>
<td>S/L</td>
<td>Del</td>
<td>Epi</td>
<td>Limited loss, but drastic methylation changes in random sequences and transposable elements (12–22%) from the maternal genome in F1 hybrids; limited reorganization after genome doubling (0.1–9%)</td>
<td>Parisod et al., 2009</td>
</tr>
<tr>
<td>Spartina anglica</td>
<td>Allo</td>
<td>S/L</td>
<td></td>
<td></td>
<td>Gene expression changes at hybridization (6.4%) and genome doubling (4.6%), with important maternal dominance</td>
<td>Chelaïfa et al., 2010</td>
</tr>
<tr>
<td>Tragopogon miscellus, T. mirus</td>
<td>Allo</td>
<td>S</td>
<td>Chrom</td>
<td></td>
<td>Aneuploidy (in 69% individuals) and translocations (in 76% individuals); only 3/68 plants exhibited the addition of the parental karyotypes</td>
<td>Lim et al., 2008; Chester et al., 2012</td>
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<tr>
<td>Tragopogon mirus</td>
<td>Allo</td>
<td>S/L</td>
<td>Gene</td>
<td></td>
<td>Protein expression changes (14.3%) in synthetic and established accessions; impact of hybridization greater than polyploidization</td>
<td>Koh et al., 2012</td>
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<tr>
<td>Tragopogon mirus</td>
<td>Allo</td>
<td>L</td>
<td>Gene</td>
<td></td>
<td>Loss of homeologous loci and changes in gene expression (mostly from T. dubius origin) in established accessions</td>
<td>Koh et al., 2010</td>
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<tr>
<td>Species</td>
<td>Auto/Allo</td>
<td>Timing</td>
<td>Structure</td>
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<tr>
<td><em>Tragopogon miscellus</em></td>
<td>Allo</td>
<td>S/L</td>
<td>Gene</td>
<td></td>
<td>Loss (0.6%, mostly paternal) and gain (1%) of cDNA fragments in synthetic and established accessions; differential expression of the parental homeologs in 1/10 candidate genes</td>
<td>Tate et al., 2006</td>
</tr>
<tr>
<td><em>Tragopogon miscellus</em></td>
<td>Allo</td>
<td>L</td>
<td>Gene</td>
<td></td>
<td>Loss (20%, mostly paternal) of homeologous gene in established accessions</td>
<td>Buggs et al., 2009, 2012</td>
</tr>
<tr>
<td><em>Triticum aestivum</em></td>
<td>Allo</td>
<td>S</td>
<td>NS</td>
<td></td>
<td>No restructuring, but aneuploidy in the first generations (S1 and S2) of synthetic accessions</td>
<td>Mestiri et al., 2010</td>
</tr>
<tr>
<td><em>Triticum aestivum</em></td>
<td>Allo</td>
<td>S</td>
<td>Epi</td>
<td></td>
<td>miRNAs increase (21–44%) and siRNAs decrease (34–12%) in synthetic accessions; siRNA repressing transposable elements downregulated in association with methylation changes at polyploidization but not hybridization</td>
<td>Kenan-Eichler et al., 2011; Yaakov and Kashkush., 2011</td>
</tr>
<tr>
<td><em>Triticum aestivum</em></td>
<td>Allo</td>
<td>S</td>
<td>Chrom</td>
<td>Epi</td>
<td>Intergenomic translocations in 15–20% of the synthetic accessions; restructuring (up to 0.5%) and methylation changes (2–8.5%) at loci adjacent to the retrotransposon Veju</td>
<td>Zhao et al., 2011</td>
</tr>
<tr>
<td><em>Triticum aestivum</em></td>
<td>Allo</td>
<td>S</td>
<td>Del, Ampl</td>
<td>Epi</td>
<td>Deletion (50% in S0) and insertion (S1) of Veju retrotransposon associated with methylation changes (43% in S0) in synthetic accessions</td>
<td>Kraitshtein et al., 2010</td>
</tr>
<tr>
<td><em>Triticum aestivum</em></td>
<td>Allo</td>
<td>L</td>
<td>Del</td>
<td>Gene</td>
<td>Parental dominance and nonadditive gene expression (up to 36.5%) in synthetic accessions (S4–S5 generations)</td>
<td>Qi et al., 2012</td>
</tr>
<tr>
<td><em>Triticum × Aegilops spp.</em></td>
<td>Allo</td>
<td>S</td>
<td>Del</td>
<td>Gene</td>
<td>Gene loss at the Hardness locus due to large genomic deletion in established accessions</td>
<td>Chantret et al., 2005</td>
</tr>
<tr>
<td><em>Triticum × Aegilops spp.</em></td>
<td>Allo</td>
<td>S</td>
<td>Del</td>
<td></td>
<td>Amplification/loss of subtelomeric repetitive sequences in synthetic accessions</td>
<td>Salina et al., 2004</td>
</tr>
<tr>
<td><em>Triticum × Aegilops spp.</em></td>
<td>Allo</td>
<td>S</td>
<td>Del</td>
<td></td>
<td>Nonrandom loss of low-copy and high-copy noncoding sequences (from 15.8% in F1 to 92% in S2) following both hybridization and genome doubling in synthetic accessions</td>
<td>Liu et al., 1998; Ozkan et al., 2001</td>
</tr>
<tr>
<td><em>Triticum × Aegilops spp.</em></td>
<td>Allo</td>
<td>S/L</td>
<td>Del</td>
<td></td>
<td>Genome downsizing in synthetic accessions similar to established accessions</td>
<td>Ozkan et al., 2003; Eilam et al., 2008, 2010</td>
</tr>
<tr>
<td><em>Triticum × Aegilops spp.</em></td>
<td>Allo</td>
<td>S</td>
<td>Del</td>
<td></td>
<td>Fragment loss (6.6–58.8%) in synthetic accessions (F1 to S4) and genomic changes in EST (40–64%) in both F1 hybrids and allopolyploids elimination of retrotransposons, but no gross chromosomal rearrangements in <em>Triticum aestivum</em>, <em>T. timopheevii</em> × <em>T. monococcum</em>, <em>T. aestivum</em> × <em>Secale cereale</em>, <em>T. monococcum</em> × <em>Aegilops tauschii</em></td>
<td>Han et al., 2003</td>
</tr>
<tr>
<td><em>Triticum durum</em></td>
<td>Allo</td>
<td>S</td>
<td>NS</td>
<td>Gene</td>
<td>Reproducible gene expression changes (2%) in established accessions due to gene silencing (75%) or gene loss; activated genes with known function were retrotransposons</td>
<td>Kashkush et al., 2002</td>
</tr>
<tr>
<td><em>Triticum turgidum</em></td>
<td>Allo</td>
<td>S</td>
<td>NS</td>
<td>Gene</td>
<td>Transcriptional activation of retrotransposon Wis 2-1A with impact on the expression of adjacent genes</td>
<td>Kashkush et al., 2003</td>
</tr>
</tbody>
</table>

**Table 1 (continued)**

| Allo = Allopolyploid; Ampl = sequence amplification; Auto = autopolyplod; Chrom = chromosomal rearrangement; Del = sequence deletion; Epi = epigenetic changes; Gene = change in gene expression; L = long term; NS = non-significant changes; S = short term; S/L = studies having examined both short- and long-term changes in synthetic and established accessions, respectively. a Short-term versus long-term genome reorganization. b Polyploidy-induced structural changes. c Polyploidy-induced functional changes. |
Mechanisms of genome reorganization (fig. 2) are possibly interconnected through cause-and-effect relationships, with restructuring events potentially having functional effects. Furthermore, activation of transposable elements likely impacts the structure and the functioning of polyploid genomes. As several studies in various species highlighted reproducible changes after independent polyploidization events, such particular modifications may be selected for, but this remains to be tested. Also, to what extent immediate genome changes support genome-wide diploidization in the longer term should be further assessed. A better understanding of the origins and consequences of genome reorganization may lead to heuristic categories of the polyploidy-induced molecular changes.

**Origins and Consequences of Polyploidy-Induced Genome Reorganization**

The formation of polyploid lineages involves the merging of more or less divergent genomes, potentially uniting incompatible loci that accumulated during the differentiation of the progenitors and resulting in hybrid sterility or inviability [Stebbins, 1958; Rieseberg, 2001b]. As incompatible chromosomal or genic combinations are unlikely to be purged through segregation in polyploids, non-Mendelian mechanisms involving genome doubling per se, genome restructuring and/or epigenetic changes may thus help restoring the fitness of the nascent polyploid [Rieseberg, 2001a].

**Chromosomal Incompatibilities and Proper Meiotic Pairing**

The merging of structurally divergent genomes induces troubles at meiosis when homeologous chromosomes do not pair properly in the F1 hybrids (i.e. chromosomal incompatibility [Rieseberg, 2001b; Grandant et al., this issue]). Accordingly, loosely paired chromosomes segregate randomly, resulting in increased frequencies of non-functional gametes and thus sterility (fig. 3A). In this context, whole genome duplication is restoring the fertility of hybrids between taxa with structurally divergent genomes, furnishing the exact complements to all chromosomes and allowing proper meiotic pairing. Unless chromosomal rearrangements further harbor genic incompatibilities [Noor and Feder, 2006; Maheshwari and Barbash, 2011], chromosomal divergence between diploid taxa thus likely promotes the origin of polyploid lineages as whole genome duplication provides pairing part-
ners to all chromosomes in hybrids and may restore their fertility [Rieseberg and Willis, 2007; Buggs et al., 2011].

Homeologous chromosomes likely display similar chromosomal regions resulting in improper pairing at meiosis and promoting intergenomic recombination and chromosomal rearrangements [Gaeta and Pires, 2010]. The processes governing meiotic pairing are not fully understood yet [Stewart and Dawson, 2008], but structural features as well as specific genetic factors, such as the Ph1 gene in wheat, are expected to promote homologous pairing [Jenczewski and Alix, 2004; Griffiths et al., 2006]. Activation of DNA recombination/repair pathways is suggested to efficiently correct non-homologous recombination in synthetic auto- and allotetraploids [Wang et al., 2004]. Restructuring events in improperly paired regions of the chromosomes may thus sustain the differentiation of homeologous chromosomes and promote strict bivalent pairing (i.e. homologous recombination) during the first generations of the diploidization process [Ma and Gustafson, 2005]. This is consistent with the elimination

**Fig. 3.** Mechanisms of genetic incompatibilities in hybrids. **A** Structural incompatibilities (here, an inversion marked by arrows) leading to hybrid sterility. **B, C** Genic incompatibilities accumulated between divergent genomes leading to dysfunctional hybrids. **D** Mismatch between transposable elements and their repressors (siRNAs) leading to the activation of transposable elements in hybrids (i.e. hybrid dysgenesis).
of sequences from homoeologous chromosome regions in both auto- and allopolyploids during cytological diploidization [Eilam et al., 2009, 2010; Feldman et al., 2012]. Nevertheless, the hypothesis that restructuring is adaptive, improving the fertility of neopolyploids, largely remains to be tested.

**Genic Incompatibilities and Their Purging**

Hybridization and genome doubling at the origin of polyploid lineages produces new combinations of interacting genes and, thereby, may reveal genic incompatibilities as well as new gene dosage configurations reducing the hybrid fitness [Maheshwari and Barbash, 2011]. The model of Dobzhansky-Muller interactions (fig. 3B) offers the classical framework to understand genic incompatibilities reducing hybrid fitness due to dysfunctional interactions among neutrally or adaptively accumulated alleles at one or several loci [Coyne and Orr, 2004]. Alternative models, such as the ‘mutation-rescue model’, may also explain genic incompatibilities, including nucleo-cytoplasmic interactions [reviewed in Nei and Nozawa, 2011].

In the context of polyploid speciation, whole genome duplication will not alleviate the effect of genic incompatibilities revealed by genome merging. Accordingly, a nascent polyploid will suffer from reduced fitness, and its genome has to be rapidly purged from incompatible loci to establish a successful lineage. As loci affecting the viability of both the hybrid and its gametes (i.e. hybrid fertility) can hardly be eliminated through segregation in a polyploid, molecular events such as sequence loss or methylation changes may, therefore, be involved as major mechanisms eliminating or silencing genic incompatibilities [Rieseberg, 2001a]. Adaptive processes may thus partly account for the patterns of genome reorganization commonly observed in nascent polyploids and explain that specific polyploidy-induced genome changes are reproducible. Such a hypothesis, however, remains largely to be tested.

**Transposable Elements and Hybrid Dysgenesis**

Transposable elements represent the major and most dynamic fraction of plant genomes [Tenaillon et al., 2010]. Accordingly, diverging taxa likely accumulate differential arrangements of transposable elements, reducing recombination and likely resulting in chromosomal incompatibilities at hybridization [He and Dooner, 2009; Abbott et al., 2013]. Such differential dynamics of transposable elements can also lead to the accumulation of different amounts or differentiated copies in divergent genomes that may reveal conflicts after genome merging as the hybrid genome fails to regulate their activity (fig. 3D).

The activity of transposable elements is indeed controlled by repressive small interfering RNA (siRNA) targeting and silencing homologous inserted copies via DNA methylation and other epigenetic marks [Bourc’his and Voinnet, 2010]. In somatic cells, siRNA and transposable elements match, ensuring proper repression and genome stability [Martienssen, 2010]. The soft reactivation of transposable elements during gametogenesis boost the production of siRNAs in accompanying cells and ensures the maintenance of repression across generations. However, cytoplasmic siRNA may fail to repress all copies after the merging of genomes presenting large divergence in their transposable elements content [reviewed in Parisod and Senerchia, 2013]. Such conflicts may even be stronger in the endosperm, where 2 maternal genomes are merged with the paternal one. The resulting activation of transposable elements during the merging of divergent genomes may lead to transposition burst and/or epigenetic repatterning, leading to developmental failure in the endosperm and deleterious mutations in the zygote (i.e. hybrid dysgenesis).

In the context of polyploid speciation, genome doubling or the purging of localized loci is unexpected to mitigate the impact of the activation of interspersed transposable elements. Successful neopolyploids have to effectively repress active transposable elements at a genome-wide scale through loss of sequences that would otherwise have proliferated and strong reorganization of epigenetic marks promoting their silencing. Accordingly, polyploidy seems to induce genome-wide restructuring and epigenetic re-patterning with genome changes specifically affecting transposable elements as soon as divergent genomes are merged [Parisod et al., 2010b]. Despite recent progresses [reviewed in Parisod and Senerchia, 2013; Bento et al., this issue], several aspects of the conflict among transposable elements and its resolution remain to be elucidated.

**Long-Term Diploidization**

Polyploidy is assumed to promote evolutionary novelties, and it is, therefore, essential to better understand the forces behind the maintenance of duplicated sequences [McGrath and Lynch, 2012]. Genome structural differentiation supports proper homologous paring (i.e. cytological diploidization) but is also suggested to facilitate functional diploidization by restricting intergenomic recombination and thus favoring the divergence of duplicated gene [Feldman et al., 2012]. Several models have been
proposed to explain the fate of duplicated genes toward either nonfunctional pseudogenes or subfunctionalyzed genes having partitioned the ancestral function or neo-functionalyzed genes with new functions [Innan and Kondrashov, 2010]. In particular, the ‘dosage balance’ hypothesis [Birchler and Veitia, 2012] seems to match observed patterns of long-term retention of dosage-sensitive genes better than the long-held hypothesis postulating relaxed purifying selection on redundant functions [Ohno, 1970; Force et al., 1999]. Whole genome duplication indeed creates whole sets of redundant functional genes that interact through proper stoichiometric relationships, representing a potentially strong constraint selecting for genome stability. Accordingly, it would be crucial to assess to what extent functional genes are differentially constrained in auto- versus allopolyploids.

Polyploidy is often considered as a mechanism of abrupt speciation [Coyne and Orr, 2004] and indeed appear as a major mechanism of speciation, accounting for at least 15% of speciation events in flowering plants [Wood et al., 2009]. However, post-zygotic barriers among ploidy levels are all but impermeable [e.g. Brochmann et al., 1992; Petit et al., 1999; Slotte et al., 2008; Chapman and Abbott, 2010], and the recurrent production of polyploid lineages may further contribute to indirect gene exchange between ploidy levels [Soltis and Soltis, 1999; Modliszewski and Willis, 2012]. In addition, recently formed polyploids must establish self-sustainable populations by colonizing new territories or persisting in sympatry with the parental populations [Levin, 2002]. Especially in the case of sympatry, neopolyploids must overcome the ‘minority disadvantage’ and then have to adapt to new niches in order to avoid competition with the parental progenitors [Levin, 1975; Felber, 1991]. In other words, nascent polyploids have to achieve complete reproductive isolation, and this could be promoted by both restructuring and functional changes. Polyploidy-induced genome reorganization improving fertility in the short-term may thus further promote reproductive isolation of the neopolyploids.

To what extent long-term diploidization fosters the diversification of established polyploids remains an open question. For instance, Oka’s model [Oka, 1957], which was later popularized as the ‘duplication-degeneracy-complementation model’ [Force et al., 1999], suggests that pseudogenization or the transposition of alternative copies of duplicated genes may lead to hybrid inviability (fig. 3C) and thus foster speciation at the polyploid level. Experimental proofs of Oka’s model were recently unraveled in Arabidopsis and rice by showing that random segregation of copies of a duplicated gene produced gametes and hybrids without functional copies, suffering from reduced fitness [Bikard et al., 2009; Mizuta et al., 2010]. In striking contrast, recent phylogenetic analyses suggest that recently formed polyploids show higher extinction rates and possibly lower net diversification rates than their diploid relatives [Mayrose et al., 2011; Arrigo and Barker, 2012]. Additional work on genome reorganization in auto- and allopolyploids as compared to diploids is needed to better understand the evolutionary consequences of polyploidy.

**Perspectives**

**Impact of Hybridization and Pathways to Polyploidy on Genome Reorganization**

Additional studies addressing the patterns and the tempo of restructuring and functional changes in auto-versus allopolyploid genomes are necessary to reach firm conclusions, but the limited evidence available in auto-polyploids suggests lower levels of genome restructuring and epigenetic changes than in allopolyploids [Parisod et al., 2010a]. Correspondingly, the relative impact of hybridization and genome doubling on the genome/transcriptome shock deserves further attention. Hybridization more than genome doubling seems to trigger quick genome reorganization [Doyle et al., 2008; Hegarty and Hiscock, 2008; Feldman et al., 2012; Parisod and Senerchia, 2013]. For instance, hybridization induced at least 5 times more structural, epigenetic and gene expression changes across the genome than chromosome doubling in Spartina anglica [Parisod et al., 2009; Chelaifa et al., 2010]. Changes in gene expression were mostly attributed to genome merging in several systems [e.g. Albertin et al., 2005; Flagel et al., 2008], but changes induced by hybridization were, to a certain extent, reversed by genome doubling in others [e.g. Hegarty et al., 2006; Xu et al., 2012b]. A better understanding of the impact of merging increasingly divergent genomes in revealing hybrid incompatibilities and inducing genome reorganization seems crucial.

In order to better understand genome reorganization in the short term, the early chain of events at the origin of a polyploid lineage may reveal crucial [Hegarty and Doyle, this issue]. Natural polyploids can indeed be formed through various pathways, potentially involving the merging of different dosage of parental genomes and different rounds of genome merging versus doubling. The exact pathway at the origin of a given polyploid may
thus play a fundamental role in triggering particular genome changes. Accordingly, allopolyploid lines of *Brassica napus* produced through somatic doubling of F1 homoploid hybrids versus pathways involving unreduced gametes showed different patterns of genome restructuring [Szadkowski et al., 2011]. In particular, patterns of genome reorganization in the polyploid formed through the fusion of unreduced gametes were similar to the changes observed in the established polyploid. Exceedingly few studies addressed the impact of the pathway to polyploidy on genome changes, but it may be fundamental. As the production of synthetic polyploids contrasts with the variety of possible pathways at the origin(s) of natural polyploids, a better understanding of the impacts of hybridization and whole genome duplication as well as the timing of these events on genome reorganization seems crucial to draw suitable conclusions from synthetic polyploids.

**Emergence of a ‘Diverge, Merge and Diverge’ Model**

The realization that the origin of almost all polyploids involves the merging of more or less differentiated genomes emphasizes the need to focus on the nature of this divergence. In particular, genome divergence goes along with the accumulation of incompatible loci, which is consistent with the declining fertility of hybrids from closely related to more divergent taxa [Grant, 1981; Rieseberg and Willis, 2007]. Nevertheless, the potential for hybridization declines relatively slowly [Levin, 2012], and genomes harboring structural, genic and/or transposable element incompatibilities can merge to form new polyploid lineages [Buggs et al., 2011; Abbott et al., 2013]. Resulting interactions between genomes potentially affect the survival, establishment and persistence of nascent polyploids in the short-term [Parisod, 2012]. Polyploid lineages are seemingly formed more commonly than established, and only those having efficiently purged incompatible loci through genome reorganization may successfully establish lasting lineages. Accordingly, selection improving hybrid fitness could promote short-term reorganization of polyploid genomes. The divergence of diploid genomes at incompatible loci may thus be a suitable predictor of polyploid genome differentiation after genome merging and ‘diverge, merge and diverge’ matches the observed genome dynamics during polyploid speciation.

Successful polyploids formed from increasingly divergent genomes are expected to show increasing levels of restructuring and epigenetic repatterning to eliminate the gradually accumulated genic incompatibilities or conflicting copies of transposable elements [Abbott et al., 2013]. Genic incompatibilities should be purged through the reorganization of specific loci, whereas incompatibilities associated with transposable elements likely induce genome-wide changes [Parisod and Senerchia, 2013]. Structural incompatibilities are also expected to drive cytological diploidization, promoting an increased number of bivalents at the expense of multivalents [Feldman et al., 2012]. However, such diploidization may depend on the impact of multivalents on fitness, and patterns of restructuring may fundamentally differ in auto- versus allopolyploids [Cifuentes et al., 2010; Parisod et al., 2010a; Soltis et al., 2010]. Cytological diploidization is still poorly understood, especially in autoploids, and both its genetic basis and adaptive value have to be firmly assessed [Le Comber et al., 2010].

‘Diverge, merge and diverge’ may be a useful metaphor, but several aspects of the relationship between divergence at the diploid level and genome reorganization at the polyploid level remain to be explored and tested. In particular, genome reorganization following the merging of diploids harboring various categories of incompatibilities may be hardly predictable [Abbott et al., 2013]. Moreover, the role of genetic drift versus selection in sorting genome changes occurring after polyploidy has to be firmly assessed. Genome reorganization may well improve the fitness of nascent polyploids, but to what extent revolutionary changes fostered by the purging of hybrid incompatibilities are reinforced to facilitate the establishment of polyploids remains an open question. Accordingly, the impact of short-term genome changes on the long-term maintenance of duplicated genes as well as the impact of long-term diploidization on the diversification of auto- versus allopolyploids should be further examined. Polyploidy is more than the reshuffling of parental genomes and thus offers promising opportunities to integrate genome and phenotypic variation within a coherent evolutionary framework [Parisod, 2012].

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References


