SHORT REVIEW

The pachytene checkpoint and its relationship to evolutionary patterns of polyploidization and hybrid sterility

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Sterility is a commonly observed phenotype in interspecific hybrids. Sterility may result from chromosomal or genic incompatibilities, and much progress has been made toward understanding the genetic basis of hybrid sterility in various taxa. The underlying mechanisms causing hybrid sterility, however, are less well known. The pachytene checkpoint is a meiotic surveillance system that many organisms use to detect aberrant meiotic products, in order to prevent the production of defective gametes. We suggest that activation of the pachytene checkpoint may be an important mechanism contributing to two types of hybrid sterility. First, the pachytene checkpoint may form the mechanistic basis of some gene-based hybrid sterility phenotypes. Second, the pachytene checkpoint may be an important mechanism that mediates chromosomal-based hybrid sterility phenotypes involving gametes with non-haploid (either non-reduced or aneuploid) chromosome sets. Studies in several species suggest that the strength of the

pachytene checkpoint is sexually dimorphic, observations that warrant future investigation into whether such variation may contribute to differences in patterns of sterility between male and female interspecific hybrids. In addition, plants seem to lack the pachytene checkpoint, which correlates with increased production of unreduced gametes and a higher incidence of polyploid species in plants versus animals. Although the pachytene checkpoint occurs in many animals and in fungi, at least some of the genes that execute the pachytene checkpoint are different among organisms. This finding suggests that the penetrance of the pachytene checkpoint, and even its presence or absence can evolve rapidly. The surprising degree of evolutionary flexibility in this meiotic surveillance system may contribute to the observed variation in patterns of hybrid sterility and in rates of polyploidization. *Heredity* (2009) **102**, 24–30; doi:10.1038/hdy.2008.84; published online 3 September 2008

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Introduction

The genetic basis of postzygotic reproductive isolation has become clearer over the last decade. Depending on the specific mechanism involved, postzygotic isolation can be due to either genic or chromosomal incompatibility. In most animals, incompatibilities mediated by deleterious interactions among genes are thought to be the primary cause of hybrid inviability and sterility, as described by Dobzhansky (1936, 1937) and Muller (1940, 1942); see also Orr and Turelli (2001). In contrast, postzygotic isolation in plants often involves karyotypic changes caused by chromosomal rearrangement or genome duplication, that is, polyploidy (Werth and Windham, 1991; Rieseberg *et al.*, 1995; Ramsey and Schemske, 1998; Comai, 2000; Lynch and Conery, 2000; Lynch and Force, 2000). However, little is known about the mechanistic basis for these incompatibilities. Here,

we discuss how a recent discovery from studies of meiotic regulation, the pachytene checkpoint, may contribute to our understanding of both chromosomal and gene-based hybrid sterility, and how the presence or absence of the pachytene checkpoint may be a critical factor in determining levels of polyploidization, a common route to speciation in plants. We also consider how sex-specific variation in the pachytene checkpoint may contribute to sex-specific patterns of variation in the penetrance of hybrid sterility.

The pachytene checkpoint

It is critical that the chromosomes carried by sperm, eggs and spores contain accurate representations of the parental genome. During meiosis, the maternal and paternal copies of each chromosome align with each other and form a synaptonemal complex, exchange genetic material through the process of recombination, and separate to daughter cells in the first of two meiotic cell divisions. These intricate chromosomal events are subject to errors; hence most organisms have evolved meiotic ‘checkpoints’ that monitor the fidelity of chromosome synapsis and the repair of DNA damage. These checkpoints cause defective meiocytes to self-destruct, thus preventing the generation of defective gametes.

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Pachytene is the stage of meiotic prophase I where chromosomes are completely aligned with their homologous partner, a process known as synapsis. In many species, including *Saccharomyces cerevisiae*, *Drosophila melanogaster*, *Caenorhabditis elegans* and mice, defects in recombination and/or synapsis lead to arrest during the pachytene stage, and arrested cells will eventually be eliminated (Bishop *et al.*, 1992; Sym *et al.*, 1993; Edelmann *et al.*, 1996; McKee and Kleckner, 1997; Chua and Roeder, 1998; Pittman *et al.*, 1998; Ghabrial and Schubach, 1999; Gartner *et al.*, 2000). This surveillance process is referred to as the pachytene checkpoint. For organisms with a strict pachytene checkpoint, triploid or trisomic individuals cannot generate gametes, and meiotic cells with pairing or recombination defects are aborted.

Evidence for different mechanisms of the pachytene checkpoint in different species

Although the pachytene checkpoint is observed in many organisms ranging from yeast to mammals, it seems that different mechanisms may be involved in different species. It has been suggested that there are at least two surveillance mechanisms that monitor meiotic chromosome metabolism in budding yeast, worms and mice. One pathway monitors recombination intermediates and the other monitors incomplete synapsis. Pachytene checkpoint genes have been most intensively studied in the budding yeast *S. cerevisiae* (reviewed in Lee and Amon, 2001). Numerous mutations have been identified that block chromosome synapsis and/or recombination and induce pachytene arrest (Roeder, 1997; Roeder and Bailis, 2000). The characterization of secondary mutations that bypass pachytene arrest in the presence of defects in recombination and synapsis has led to the identification of pachytene checkpoint genes (reviewed in Roeder and Bailis, 2000). For example, in *S. cerevisiae*, *PCH2* was identified in a genetic screen for mutations that bypass the pachytene arrest triggered by deletions of genes such as *ZIP1* (which encodes a synaptonemal complex central element component) (San-Segundo and Roeder, 1999). In this species, several genes involved in the mitotic DNA damage checkpoint also participate in the pachytene checkpoint to monitor the presence of recombination intermediates (Lydall *et al.*, 1996; Leu and Roeder, 1999; San-Segundo and Roeder, 1999; Hochwagen *et al.*, 2005; Hochwagen and Amon, 2006). However, in mammals, the somatic checkpoint and pachytene checkpoint might use different genes. For example, *Atm*-deficient somatic cells are highly resistant to radiation-induced apoptosis (Xu and Baltimore, 1996), whereas meiocytes in *Atm*-null mice can still trigger the pachytene checkpoint and undergo apoptosis (Barlow *et al.*, 1998).

Genetic studies of *S. cerevisiae* and the nematode *C. elegans* have indicated that *PCH2* is required for a checkpoint that monitors defects in synapsis, but not DNA damage (Bhalla and Dernburg, 2005; Wu and Burgess, 2006). *PCH2* orthologs have been found in many organisms (Wu and Burgess, 2006; Li and Schimenti, 2007), suggesting that synaptic checkpoints might be conserved across taxa. However, recent studies indicate that the *PCH2* ortholog (called *Trip13*) in mice seems to not play a role in pachytene checkpoint control (Li and

Schimenti, 2007). Furthermore, most of the other synapsis checkpoint genes identified in yeast do not have orthologs in mammals. These findings suggest that the 'pachytene checkpoint' has evolved independently in different organisms.

Evidence for differences in the strictness of the pachytene checkpoint in different sexes

Mouse meiotic mutants exhibit significant sexual dimorphism attributable to differential sensitivity of meiotic checkpoints (Hunt and Hassold, 2002). Spermatocytes are sensitive to mutations that disrupt either recombinational double-strand break repair or synapsis. In contrast, although oocytes are efficiently eliminated in response to unrepaired DNA damage, they are less sensitive to incomplete synapsis (Yuan *et al.*, 2000; Hunt and Hassold, 2002; Barchi *et al.*, 2005; Di Giacomo *et al.*, 2005).

Sexual dimorphism has also been observed in triploids. Interestingly, triploid chickens (which have ZW chromosomes) have reversed sexual dimorphism compared with mice (which have XY chromosomes). In triploid chickens, most oocyte loss occurs in young females a few weeks after hatching, probably as a consequence of the pachytene checkpoint. However, spermatocytes from male triploids can complete meiosis without delay. Although these spermatocytes do not form fully functional sperm, they do reach the advanced stage of round spermatids (Lin *et al.*, 1986).

The frog, *Buergeria buergeri* (Anura, Rhacophoridae), also has a ZW sex chromosome system and seems to have a less strict meiotic checkpoint in males. Ohta *et al.* (1999) found that all ZWW-type triploid frogs were females having small ovaries, and oocytes were scarce and small. However, there was little difference in the number of germ cells compared with normal diploid females, suggesting that a checkpoint is blocking meiosis. In contrast, all ZZZ-type triploid frogs were males, and their testes produced spermatozoa. These spermatozoa did show some minor defects, being somewhat long and thick when compared with spermatozoa produced by diploid males (Ohta *et al.*, 1999). Nevertheless, the presence of spermatozoa indicates that meiosis was not aborted in these triploid males.

Because asynapsis normally triggers the pachytene checkpoint, the heterogametic sex with distinctive heteromorphic sex chromosomes must evolve a mechanism to suppress detection of asynapsis. The failure of such a mechanism would trigger the checkpoint only in the heterogametic sex, which may underlie the examples of sexual dimorphism described above. During meiotic prophase in male mammals, meiotic sex chromosome inactivation causes the X and Y chromosomes to be incorporated into the heterochromatinized XY body (also called the sex body) (Handel, 2004; Turner *et al.*, 2006). It has been suggested that the failure of meiotic sex chromosome inactivation may trigger apoptosis of defective spermatocytes (Turner *et al.*, 2005), since in most meiotic mutants and sterile hybrid mice, the formation of the XY body is disrupted (Fernandez-Capetillo *et al.*, 2003; Turner *et al.*, 2005; Homolka *et al.*, 2007). In ZW female birds and snakes, although the W chromosome is not silenced, it has been shown that the

unpaired regions are thickened and become partially heterochromatic (Forejt and Gregorova, 1977; Becak and Becak, 1981). Both the meiotic sex chromosome inactivation of the XY chromosomes and heterochromatinization of the remaining unpaired ZW regions may provide the mechanisms to suppress their intrinsic asynapsis (Jablonka and Lamb, 1988). Organisms with homomorphic sex chromosomes do not face an intrinsic asynapsis problem, so they may not have a stricter pachytene checkpoint in the heterogametic sex. If so, then we would predict that sexual dimorphism in the degree of sterility in triploids will be more pronounced in species that have older, more differentiated sex chromosomes.

These examples bear similarity to Haldane's rule, which describes the observation that the heterogametic sex (XY or ZW) is more likely to show hybrid lethality or sterility than the homogametic sex (XX or ZZ) (Haldane, 1922). Haldane's rule is likely to reflect several underlying causes, including the recessivity of hybrid incompatibility genes, the higher accumulation of such genes on the X chromosome, and the higher rate of evolution of male versus female hybrid sterility genes (Wu and Davis, 1993; Masly and Presgraves, 2007). As the last explanation would counteract Haldane's rule in ZW species where females are preferentially sterile or lethal, more research is needed to understand the mechanistic basis of sterility in ZW females of species such as birds (Price and Bouvier, 2002) and Lepidoptera (Presgraves, 2002). Finally, we suggest that sexual dimorphism in the pachytene checkpoint is one promising direction for future research.

However, we note that even if sexual dimorphism is found in additional ZW species it cannot be the sole determinant of Haldane's rule. Haldane's rule does not hold in diploid *Xenopus*, with all described interspecific crosses producing sterile hybrid males and fertile hybrid females (Kobel, 1996). Therefore, if male *Xenopus* do have a weaker pachytene checkpoint, as the data from triploid taxa suggest, then this difference is clearly not causing the sex-specific differences in hybrid sterility. The violation of Haldane's rule may reflect the fact that most amphibian species do not have morphologically distinct sex chromosomes (Eggert, 2004). A recent study suggests that this preferential male sterility is caused by spermatogenesis being more sensitive to disruption in hybrids compared with oogenesis (Malone and Michalak, 2008). This finding is consistent with an earlier hypothesis for why males evolve hybrid sterility faster than females (Wu and Davis, 1993). It will be interesting to evaluate at which stage spermatogenesis is blocked in the *Xenopus* hybrid males and to determine whether they have a meiotic or post-meiotic defect.

The pachytene checkpoint contributes to the speciation process by preventing hybrids from reproducing

Although many cases of sterile hybrids have been described, the underlying causes of sterility have typically been investigated using classical genetic or cytological methods only, or remain entirely unknown. Indeed, the pachytene checkpoint has only recently been described and investigated on a molecular level. Here, we describe a few examples of hybrid sterility that may

reflect the activity of the pachytene checkpoint. When doing so, it is important to distinguish between the terms 'sterile' and 'infertile.' Sterile refers only to situations in which no gametes are produced, whereas infertile refers to situations in which gametes are produced, but they are nonfunctional (or sub-functional). These phenotypes are likely triggered by different mechanisms. Sterility of hybrids may potentially result from activation of the pachytene checkpoint, whereas infertility of hybrids is more likely owing to other types of surveillance mechanisms, such as those that sense dosage effects because of aneuploidy or structural defects in gametes. We suggest two ways in which consideration of the pachytene checkpoint may be helpful in understanding hybrid sterility. The first is a mechanism that may be triggered by the action of hybrid incompatibility genes. We emphasize that there is unlikely to be a single mechanistic explanation for genic hybrid incompatibility phenotypes. The second may reflect a more central role of the pachytene checkpoint in sensing chromosomal incompatibilities.

The pachytene checkpoint and genic incompatibilities

Hybrid sterility in mammals has been well-studied in rodents (Forejt, 1996; Borodin *et al.*, 1998, 2006), where it shows a clear pattern of pachytene checkpoint effects. Female hybrids are mostly fertile, whereas male hybrids are sterile with meiotic arrest around pachytene (Forejt and Ivanyi, 1974; Yoshiki *et al.*, 1993). Aberration of chromosome pairing has been detected at the pachytene stages of hybrid male mice (Chandley, 1988). Apparently, asynapsis in the hybrids triggers checkpoint effects.

Nevertheless, detailed studies indicate that genic incompatibility also contributes to hybrid sterility. The ability of certain chromosome rearrangements to pass through meiosis depends on the genetic background (de Boer and de Jong, 1989; Speed, 1989). In hybrids between two races of the house shrew *Suncus murinus* that differ by five Robertsonian translocations, heterozygotes for each of the translocation chromosomes that distinguish the two parental races were found in both sterile and fertile males (Borodin *et al.*, 1998), suggesting that chromosomal differences cannot be the sole cause of sterility. In another study, there was no apparent pairing defect in the male hybrids between *Thrichomys apereoides* subsp. *apereoides* and *T. apereoides* subsp. *laurentius*, but no spermatocytes beyond diplotene were detected, suggesting that the pachytene checkpoint is activated. This meiotic disruption phenotype segregates during backcrossing in males with homomorphic karyotypes, again suggesting a genic rather than chromosomal basis for sterility (Borodin *et al.*, 2006). Thus far, five hybrid sterility (*Hst*) loci have been identified in the mouse genome (Forejt, 1996), but the genes have not been identified. *Hst1*-dependent sterility causes arrest at the pachytene stage (Forejt, 1996), which suggests that pachytene checkpoint pathways may be involved. It also might be the case that only certain regions in the genome, possibly the *Hst* loci, work as sensors to monitor the pairing, and are able to trigger the pachytene checkpoint. Other hybrid male sterility phenotypes seem to manifest post-meiotically (Good *et al.*, 2008); hence, pachytene arrest is clearly not the sole cause of mouse hybrid sterility.

The pachytene checkpoint and chromosomal incompatibilities

Chicken–pheasant hybrids are viable but sterile with a meiotic disruption. Stages beyond primary spermatocytes are not present, indicating the likely role of the pachytene checkpoint in hybrid sterility (Purohit and Basrur, 1977). Cytological studies indicate that the Z chromosomes of chickens and pheasants seem to be identical between the species, whereas the autosomal complements are radically different (Stenius *et al.*, 1963), suggesting that chromosomal incompatibilities are responsible for hybrid sterility.

Two well-known examples of sterile hybrids are hinnies, from crossing male horses with female donkeys, and mules, from crossing female horses with male donkeys. Karyotypic dissimilarities exist between the horse (64 chromosomes), the donkey (62 chromosomes) and the ensuing hybrids (63 chromosomes), helping to explain why hybrids are typically sterile. The first mechanistic explanation of a male mule's sterility was provided by Wodsdalek (1916) who concluded that there was a block in meiosis. More recent cytological studies by electron microscopy of the mule testes have shown that spermatogenesis can only reach the pachytene stage, at which time degenerative changes occur (Hernández-Jáuregui and Márquez Monter, 1977). In female mules and hinnies, there is also a severe depletion of oocytes in the ovaries, with most oocytes being rapidly eliminated after birth (Taylor and Short, 1973), which is around the pachytene stage. These data strongly suggest that meiocytes in mules are eliminated by the mammalian pachytene checkpoint. Interestingly, there is also a block in spermatogenesis at the pachytene stage of meiosis in the testes of zebra–horse and zebra–donkey hybrids, where the karyotype differences between the parental species are even greater (King *et al.*, 1965).

In reptiles and fish, hybrid triploids are often formed and the triploid females are sterile. For example, triploids induced in the hybrid sturgeon (*Huso huso* female crossed to *Acipenser ruthenus* male) are sterile because they are unable to complete meiosis (Omoto *et al.*, 2005). Another example is the diploid unisexual lizard *Aspidozelis dixonii*. *A. dixonii* normally reproduces parthenogenetically but it can mate with males from the bisexual species *A. tigris punctilinealis*. The resulting triploid female hybrids are sterile (Cole *et al.*, 2007). Interestingly, triploid parthenogenetic species have evolved multiple times within this genus (Reeder *et al.*, 2002). For example, in triploid *Cnemidophorus uniparens* females the pachytene checkpoint is overcome by premeiotic endoduplication (Cuellar, 1971). This override presumably occurs because after premeiotic endoduplication the 6N meiocytes are able to synapse better than 3N meiocytes.

The absence of the pachytene checkpoint—a potential factor contributing to the high frequency of polyploidization in plants

The pachytene checkpoint has not been found in plants. Most plant meiotic mutants complete meiosis and

cytokinesis and produce abnormal microspores (Caryl *et al.*, 2003). It is uncertain whether the pachytene checkpoint was initially present and then lost during plant evolution, although it does not occur in at least one basal species, the green algae *Chlamydomonas reinhardtii*. Triploid *C. reinhardtii* zygotes formed from a haploid–diploid mating can produce viable spores (Dutcher, 1988).

A major consequence of the lack of a pachytene checkpoint in plants is that, in contrast to the frequent sterility of hybrid animals, hybrid plants are generally able to produce gametes. However, a relatively large proportion of gametes produced by hybrid plants are either unbalanced (leading to infertility) or unreduced (that is, containing the somatic chromosome number). Indeed, the mean estimates of unreduced gamete production are as high as 27.52% in hybrid taxa compared with 0.56% in nonhybrids (Ramsey and Schemske, 1998). As Levin (2002) points out, this represents a nearly 50-fold increase in the production of unreduced gametes among hybrid relative to non-hybrid taxa, and is likely because of a high incidence of meiotic irregularities in the former relative to the latter. The production of unreduced gametes can result in decreased fertility when most conspecifics are producing normal, reduced gametes. In this situation, the reduction in fertility occurs because the fusion of unreduced (for example, $2n$) and reduced (for example, $1n$) gametes produce zygotes with uneven chromosome numbers (for example, $3n$). However, if multiple individuals within a population are producing unreduced gametes, or if a single individual producing unreduced gametes reproduces through self-fertilization, viable zygotes containing twice the number of chromosomes as their parents (that is, polyploids) can be formed.

Polyploidy can arise through the doubling of chromosomes in somatic cells or through the union of unreduced gametes (deWet, 1980; Ramsey and Schemske, 1998; Levin, 2002). For many years, it was believed that somatic chromosome doubling was the predominant mode of polyploid formation, because the production of unreduced gametes was thought to be relatively rare. However, we now know that the production of unreduced gametes is more common than previously believed, and that their union is a common route to the evolution of polyploid lineages (Harlan and deWet, 1975; Bretagnolle and Thompson, 1995; Ramsey and Schemske, 1998). Unreduced gametes can arise because of errors at several points during meiosis, but the majority occur after pachytene checkpoint. Therefore, in terms of its influence on the evolution of polyploidy in plants, the lack of the pachytene checkpoint is probably most important when unreduced gametes arise as a result of what Lelley *et al.* (1987) and Bretagnolle and Thompson (1995) call 'premeiotic doubling'. For this reason, the lack of the pachytene checkpoint might provide one of several distinct mechanistic explanations for the ability of plants to initially establish polyploidy at high frequency relative to other taxonomic groups. In conclusion, the lack of a pachytene checkpoint can potentially contribute to polyploidy in two ways. First, it allows the survival of unreduced gametes from premeiotic doubling (or other events that produce unreduced gametes before or during pachytene). Second, it allows newly formed polyploids and hybrids to produce gametes, facilitating the

maintenance and long-term persistence of polyploid populations.

The absence of a pachytene checkpoint may also promote intraspecific variation in plants compared with animals by increasing the tolerance for sequence divergence. In animals, the pachytene checkpoint effectively prevents interspecific gene flow. For plants, however, meiosis can proceed in hybrids even if relatively high sequence divergence causes asynapsis between chromosomes from the two parental strains or species. Thus, the absence of a pachytene checkpoint may help to explain high levels of variation in some plants, for example, the finding that two lineages of maize are, on average, as genetically diverged as humans and chimpanzees (Buckler *et al.*, 2006).

Do animal polyploids lack the pachytene checkpoint?

Polyploidy is relatively rare in most groups of animals. However, there is increasing evidence that in some groups of animals polyploidy is more frequent than previously believed (Bogart, 1980; Lokki and Saura, 1980; Schultz, 1980; Otto and Whitton, 2000; Gallardo *et al.*, 2004; Le Comber and Smith, 2004; Mable, 2004). As the pachytene checkpoint effectively eliminates the production of unreduced gametes in animals, we might expect that, relative to plants, a higher proportion of polyploid animals are formed through mitotic duplication (that is, endoduplication). Interestingly, this prediction is consistent with the observation that the majority of polyploid animals reproduce parthenogenetically, and the evolution of parthenogenesis in animals typically predates polyploidy (Suomalainen *et al.*, 1987; Otto and Whitton, 2000). These findings raise two major questions. First, what accounts for the general difference in rates of polyploidization between plants and animals? Second, what accounts for the relatively high incidence of polyploidy in certain animal groups?

A number of explanations have been suggested to account for these patterns (Muller, 1925; Orr, 1990; Mable, 2004). We suggest that the lack of a pachytene checkpoint in plants is an additional explanation for the first question of why polyploidy is generally more common among plants. How do we account for the presence of polyploid animals among some insects, reptiles, amphibians and fish? One possibility is that these polyploid animals have lost the pachytene checkpoint genes that are present in their non-polyploid sister taxa. This scenario would imply that polyploid animals would proceed through meiosis even when subject to various meiotic defects. Indeed, as we have noted, the pachytene checkpoint is sexually dimorphic in some species, which demonstrates that variability in the penetrance of the pachytene checkpoint can be tolerated within species.

Alternatively, these animal polyploids may have evolved mechanisms to override the ability of the pachytene checkpoint to detect or respond to the presence of non-haploid gametes, as in the case of premeiotic endoduplication. This scenario would also imply that polyploids retain the ability to arrest meiotic products that have received other types of DNA damage. Analysis of the pachytene checkpoint in the model

organisms zebrafish (*Danio rerio*) and *Xenopus* frogs (*Xenopus laevis*) will provide useful data for launching comparative studies of polyploid fish and amphibians to investigate whether and how they have evolved the ability to produce non-haploid gametes.

In conclusion, the pachytene checkpoint is not only a surveillance system in meiosis. We suggest that the presence or absence of a pachytene checkpoint has a profound influence on the evolutionary strategies of different eukaryotic groups, and of the different sexes. On the basis of evidence reviewed here, we can make two conclusions. First, the pachytene checkpoint is the underlying mechanism for hybrid sterility in some cases, but more cytological evidence on additional hybrids is required to assess the generality of this finding. Second, the absence of a pachytene checkpoint in plants might influence the production and/or survival of unreduced gametes and allow newly formed polyploids and hybrids to produce viable gametes, facilitating the maintenance and long-term persistence of polyploid populations. Further research on polyploid animals is one direction that we suggest will help to test this hypothesis. The finding that different organisms seem to use different genes to execute the pachytene checkpoint underscores the evolutionary lability of this meiotic surveillance system, and calls for the further study of the molecular mechanisms controlling the pachytene checkpoint in different organisms.

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