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Beyond speciation genes: an overview of genome stability in evolution and speciation

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Abstract

Genome stability ensures individual fitness and reliable transmission of genetic information. Hybridization between diverging lineages can trigger genome instability, highlighting its potential role in post-zygotic reproductive isolation. We argue that genome instability is not merely one of several types of hybrid incompatibility, but rather that genome stability is one of the very first and most fundamental traits that can break down when two diverged genomes are combined. Future work will reveal how frequent and predictable genome instability is in hybrids, how it affects hybrid fitness, and whether it is a direct cause or consequence of speciation.

Introduction

Speciation is the biological process by which populations diverge and become reproductively isolated. Much work has been devoted to identifying hybrid incompatibility genes that underlie reproductive isolation. Only a handful have been identified, highlighting firstly the confounding effect of other processes producing similar signatures of high divergence (e.g. drift and linked selection) and secondly the complex genetic basis of reproductive isolation [1,2]. Massively parallel sequencing has greatly improved our understanding of the genomic landscape of DNA sequence divergence and speciation [3]. One surprising finding is that there seems to be only rare instances where diverging populations carry differentially fixed alleles of genes involved in post-zygotic reproductive isolation [1,4]. This is because evolution and divergence seem to proceed mainly by soft sweeps from standing genetic variation and reproductive isolation tends to be highly polygenic. This also explains why so few “speciation genes” (more accurately termed “reproductive isolation genes”) have been identified outside of model systems [2,5]. The molecular basis of post-zygotic reproductive isolation thus remains difficult to identify using current strategies.

Here, we suggest that a focus on genome stability will be a fruitful strategy to tackle the molecular and genetic basis of post-zygotic reproductive isolation. Processes that maintain genome stability have frequently been observed to be “broken down” in hybrids, causing

sterility and/or lethality through increased mutation rate or inaccurate chromosome segregation ([2,6–8] and references discussed below). This is because genomes are co-evolved units influenced by selective and neutral processes, and hybridization may disrupt this co-adaptation, leading to genome instability in multiple, additive and non-additive ways. We thus view genome stability as a trait, and genome instability as a hybrid incompatibility phenotype, with the underlying cause being sequence divergence and/or genome rearrangements between hybridizing populations or species. We suggest that genome instability is a widespread hybrid incompatibility phenotype because of the range of sequence classes whose divergence leads to genome instability. We present and discuss six mechanisms by which genome instability may arise in hybrids (Figure 1). Examples from the current literature illustrate how these mechanisms relate to divergence and how they may have genetic architectures of variable complexity. Finally we raise important questions to be addressed by future studies.

Genome stability is a complex trait

We consider genome stability as a trait with a complex genetic basis which requires a tight coordination of a complex network of signaling pathways [9]. Genome instability can arise from intrinsic factors such as transposable element derepression or mitochondrial metabolism, and from extrinsic factors such as environmental mutagens [9]. Therefore, genome instability may also involve gene-environment interactions. Molecular processes underlying genome stability include DNA damage sensors, DNA repair pathways and cell cycle checkpoints [9]. A major structural feature of genome stability is heterochromatin, a specialized type of chromatin that maintains repetitive DNA in a silent state. Heterochromatin is particularly important at telomeres and centromeres to stabilize chromosomes and maintain proper segregation [10].

The rate of sequence evolution of proteins involved in genome stability maintenance greatly varies. Many are highly conserved, sometimes from prokaryotes to eukaryotes (e.g. the recombinases *recA* and *RAD51* [11]). Others, such as some genes required for centromere assembly, telomere capping and silencing of transposable elements evolve rapidly, sometimes under positive selection [12–14]. These rapidly evolving genes are good candidates when trying to identify the molecular basis of genome instability associated with reproductive isolation, as exemplified by genes such as *PRDM9* in mammals (see below). Elucidating the forces driving rapid evolution of these genes is an important step to understanding why and how genome instability occurs in hybrids (Box 1).

Box 1

Relevant questions to genome stability and reproductive isolation

General Questions

- How frequently are hybrid genomes destabilized? Is this predictable from levels of DNA sequence divergence?

- Why are certain genes involved in genome stability highly constrained (e.g. meiotic recombination machinery) while are others rapidly evolving (e.g. centromere definition, telomere capping)?

Questions related to molecular mechanisms

- Do mito-nuclear incompatibilities lead to an increased mutation rate in hybrids?
- Is there a “divergence threshold” disrupting meiosis through MMR that is strictly DNA sequence dependent?
- Do hybrids show an increased mutation rate compared to parental lineages? Does this result from decreased replication fidelity?
- Does DNA repair pathway choice during meiotic recombination impact divergence and reproductive isolation?
- Are crossovers positioned differently in hybrids compared to parental lineages? Does this impact reproductive isolation?
- How frequent is chromosome instability in hybrids?
- Is transposable element derepression in hybrids a cause or a consequence of lineage divergence?

Mechanism 1: Mito-nuclear incompatibilities

Mitochondria produce ATP, the cell’s main source of energy, through oxidative phosphorylation. In animals, the mitochondrial genome is rapidly evolving compared to the nuclear genome [15], yet it codes for only a few genes and most proteins necessary for mitochondrial functions are encoded by the nuclear genome [16]. Therefore, the mitochondrial and nuclear genomes are thought to be tightly co-evolving within a species, and mito-nuclear incompatibilities have thus been predicted to underlie reproductive isolation [see 15 for a recent comprehensive review]. One way mito-nuclear incompatibilities could cause genome instability is by suboptimal electron transport resulting from the combination of maladapted alleles in a hybrid background. An increase in reactive oxygen species due to reduced respiratory activity occurs in mouse cybrid cell lines (cell lines which have different mtDNA haplotypes in an otherwise identical nuclear background) [17]. This may increase the amount of reactive oxygen species produced, a normal by-product of oxidative phosphorylation, but also potent DNA damage-inducing agents (Figure 1A) [15,18].

Geographically isolated populations of the marine copepod *Tigriopus californicus* exhibit a gradient of low to high levels of nuclear and mtDNA divergence (up to 15%), yet their hybrids are often at least partially viable. Barreto and Burton found that the fecundity of hybrids between increasingly divergent populations is correlated with 8-OH-dG levels, a marker of oxidative DNA damage induced by reactive oxygen species [19]. Hybrids from highly diverged populations also consistently show high 8-OH-dG levels, consistent with increased reactive oxygen species production due to sub-optimal electron transport.

Similarly, Chang et al. reported reduced fertility in *Caenorhabditis briggsae* inter-population hybrids, which correlated with increased reactive oxygen species production [20]. Considering the number of systems where mito-nuclear incompatibilities have been reported (e.g. *Drosophila* [21], *Nasonia* wasp [22], *Mimulus* monkeyflower [23], and *Anguilla* eels [24]), we predict that increased reactive oxygen species production in hybrids may be found more widely. It would be interesting to test whether increased reactive oxygen species correlate with an increased mutation rate in hybrids, which would more directly indicate genome instability due to mitochondrial dysfunction (Box 1).

Mechanism 2: DNA repair incompatibilities

Mismatch repair (MMR) proteins dramatically increase DNA replication fidelity by excising DNA mismatches that form as the result of DNA polymerase mis-incorporation errors. The MMR pathway also prevents recombination between divergent DNA sequences by recognizing and unwinding heteroduplex DNA that contains mismatches. This seems to occur during meiosis in hybrids between diverging yeast strains and species [25,26]. To our knowledge, the impact of sequence divergence has not been directly tested in other systems, but meiotic recombination may be inhibited in hybrids between diverged species, such as between the nematodes *Caenorhabditis briggsae* and *C. nigoni* [27]. These observations raise the possibility that sequence divergence *itself* may further promote divergence by inhibiting recombination through the activation of the MMR pathway (Box 1, Figure 1B). Species with exceptionally high levels of standing genetic variation, such as *C. brenneri*, may target the meiotic recombination machinery to loci with locally reduced polymorphism [28]. Another prediction is that incompatible MMR alleles could lead to a mutator phenotype, triggering genome instability in hybrids [29].

Recent studies have identified such incompatible alleles of MMR proteins. Demogines et al. [30] found that recombinant *Saccharomyces cerevisiae* strains carrying incompatible alleles of MMR proteins displayed increased mutation rates (although these strains are not reproductively isolated *per se*). Interestingly, this increased mutation rate accelerates adaptation to a stressful environment [31]. However, a mutator phenotype is predicted to be costly in the long term, due to the accumulation of deleterious mutations. Suppressor mutations within strains carrying incompatible alleles are thus likely to arise [32,but see 33 for a different interpretation]. This example illustrates how DNA repair pathways can be involved in reproductive isolation and potentially in adaptation. Considering the numerous factors influencing DNA replication fidelity [34], direct assessment of hybrid mutation rates compared to parental lineages is again likely to be an important step in deciphering such types of incompatibilities (Box 1). More detailed analyses of mutation type and context will help reveal the precise pathways involved.

Mechanism 3: Meiotic homologous recombination breakdown

Meiotic recombination directly influences eukaryotic evolution and is also generally a prerequisite to proper chromosome pairing and segregation [35]. Meiotic recombination requires the tight coordination of several steps, including homolog pairing, DNA double-strand break generation, homologous chromosome invasion, and DNA repair pathway

choice and resolution. Reproductive isolation has been associated with the breakdown of several steps of meiotic recombination, including invasion and pathway choice (MMR incompatibility described above) and possibly double-strand break generation (see below), all of which may lead to genome instability.

PRDM9 is the only known mammalian hybrid incompatibility gene [36]. PRDM9 is a histone methyltransferase which directs the meiotic homologous recombination machinery to specific sites, determining recombination hotspot usage [37]. *PRDM9* is particularly interesting because it is at the interface between recombination, chromatin modification, and chromosome segregation, emphasizing the multi-faceted aspect of genome stability. In male hybrids between *Mus musculus musculus* and *M. m. domesticus*, *PRDM9*-mediated meiotic arrest causes sterility by an unknown mechanism which relies on the DNA binding properties of PRDM9 [38], but may not involve hotspot determination [39,40]. Clearly, much remains to be discovered to understand the molecular mechanisms and genetic architecture underlying *PRDM9*-mediated hybrid infertility. More generally, there is considerable variation in how meiosis is coordinated and achieved across taxa [41,42]. For example, many organisms lack canonical hotspots (e.g. Drosophila [43]), and even within mammals, dogs and their relatives have lost *PRDM9* [44,45]. A more general research avenue is to study how DNA repair pathway choice (homologous recombination *versus* gene conversion [46]) and crossover localization [3] influence divergence and speciation across a broad range of organisms (Box 1).

Mechanism 4: Chromosomal instability and aneuploidy in hybrids

Polymorphic chromosome rearrangements such as inversions and Robertsonian rearrangements (fusions and fissions involving an entire chromosome arm) are frequently found across eukaryotes [6,7]. Chromosome rearrangements have long been hypothesized to promote divergence by reducing fitness in hybrids, but such models suffer from a theoretical conundrum regarding the small probability of fixation of rearrangements that are deleterious in heterozygotes. More recently, inversions were proposed to bolster adaptation by limiting recombination, without necessitating reduced hybrid fitness [47,48].

The house mouse *Mus musculus* is perhaps the best-characterized model supporting a role for chromosome rearrangements in post-zygotic reproductive isolation. Extensive Robertsonian rearrangements are found in *Mus musculus*. Complex and unstable meiotic chains form in hybrids between chromosomal races, leading to meiotic nondisjunction and sterility (Figure 1C) [49]. Recent work combining genetic and simulation studies shows that hybrid meiotic breakdown itself explains reductions in gene flow between rearranged chromosomes and does not require recombination suppression mechanisms [50]. Robertsonian rearrangements can impact centromere strength [51], favoring the transmission of the rearranged chromosome during the asymmetrical female meiosis (i.e. meiotic drive), and thus spreading to entire populations [52].

In the yeast *S. paradoxus* hybrids between diverging populations with rearranged chromosomes show chromosome instability [53]. Interestingly, hybridization also potentially led to speciation of a hybrid lineage in which chromosome rearrangements partially explain

reproductive isolation with ancestral lineages [54]. Recently diverged populations of Lake Whitefish (<12–15,000 generations) show evidence of ongoing chromosomal divergence, and their hybrids suffer from extensive aneuploidy consistent with both meiotic and mitotic segregation errors [55,56]. Future efforts should aim in more systems to characterize genome organization comprehensively and to document the impact of chromosome rearrangements.

Mechanism 5: Heterochromatin divergence

Heterochromatin patterns and associated DNA sequences evolve rapidly and yet contribute to essential processes such as transposable element repression and chromosome segregation. This paradox led to the hypothesis that heterochromatin differences between diverging lineages may contribute to reproductive isolation [8]. Studies in hybrids from plants to mammals show aberrations in heterochromatin such as DNA methylation patterns [57,58] which may destabilize the genome [7].

Repetitive DNA sequences such as satellite repeats are prime candidates to trigger genome instability in hybrids. Heterochromatin differences directly cause reproductive isolation between *D. simulans* females and *D. melanogaster* males, where female F1 hybrids die during embryonic development. A large block of a 359bp satellite repeat on the X chromosome of *D. melanogaster* leads to mitotic instability in female hybrids [59]. This is thought to result from improper peri-centromeric heterochromatin formation, a hypothesis supported by recent work showing that peri-centromeric satellite repeat transcription is essential for proper chromosome segregation [60]. Heterochromatin-embedded sequences are challenging to study, but emerging long-read sequencing technologies combined with complementary approaches will help reveal whether these rapidly evolving structures are frequently disrupted in hybrids (Box 1 and 2).

Box 2

Technologies to detect genome instability in hybrids

The combination of classical and state-of-the-art technologies helps is necessary to detect genome instability. Particularly challenging is the analysis of the non-coding fraction of the genome associated with heterochromatin, which is often involved in genome instability.

- **Long read sequencing**: Repetitive sequences are challenging to resolve with short reads and may result in gaps and collapses of the assembly. Long read sequencing technologies at high coverage are starting to decipher the non-coding fraction of the genome and reveal its complex organization [e.g. 68].
- **Optical mapping:** Draft genome assemblies are typically fragmented and incomplete. In optical mapping, long DNA molecules are digested with a site-specific nicking endonuclease and fluorescent probes are inserted. The resulting fluorescent molecule can be imaged and used to anchor and assemble contigs and scaffolds [e.g. 69].

- **Cytometry and "cytogenomics":** These methods allow the detection and characterization of genome size variation that may result from chromosome instability, repeat expansion or facultative chromosome polymorphism. These methods are generally inexpensive and can be integrated with genomic data [e.g. 55, 70]
- **RNA-sequencing:** When properly designed, RNA-sequencing allows to test for differential gene expression in hybrids, to characterize genetic divergence between populations and to identify candidate genes that are rapidly evolving.

Mechanism 6: small RNAs and transposable elements

Small RNAs perform multiple functions that are fundamental to genome stability, from gene expression regulation to heterochromatin assembly and dosage compensation – many of which have been reported as "broken down" in hybrids (previous section and [61]). The diverse functions of small RNAs have been extensively reviewed elsewhere [e.g. 62]; here we briefly cover their role in transposable element repression and reproductive isolation.

Transposable elements (TEs) are selfish genetic parasites found in most (if not all) eukaryotic genomes. Transposable elements must be tightly controlled, as their mobilization may lead to highly mutagenic events by creating DNA double-strand breaks, interrupting open reading frames, deregulating gene expression, and causing ectopic recombination. Transposable element repression is initiated in part by maternal loading of PIWI interacting small RNAs (piRNAs) into the egg. When there is a mismatch between paternally transmitted transposable elements and maternally loaded piRNAs, this can lead to transposable element derepression, at least in Drosophila (Figure 1D). Transposable element derepression has frequently been reported in hybrids [e.g. 63–66].

There is an ever growing list of host-encoded transposable element repressors, many of which are rapidly evolving [67]. These are good candidates in the search for the molecular basis of reproductive isolation associated with genome instability, because divergent alleles may be incompatible, triggering transposable element derepression in hybrids. One test of this hypothesis, however, found surprisingly mild effects on TE expression when the *D. melanogaster aubergine* gene was replaced by its *D. simulans* ortholog [64].

Emerging conclusions and moving forward

The examples discussed herein illustrate three key points. First, integrative studies are needed to tackle the molecular basis of post-zygotic reproductive isolation and speciation. Post-zygotic reproductive isolation is difficult to observe in the wild, and understanding its mechanisms requires the integration of data from natural populations with carefully controlled laboratory studies. Best-understood examples come from model organisms, but pioneering work has also been done in non-classical genetic systems such as sticklebacks, the monkey flower Mimulus, Helianthus sunflowers, and the Lake Whitefish. Further integrative work in a broad taxonomic range should be encouraged. Second, the genetic changes contributing to lineage divergence and post-zygotic reproductive isolation can be

associated with non-coding DNA, which is a substantial and rapidly evolving part of the genome. Emerging technologies will help reveal which changes destabilize hybrid genomes and how they do so (Box 2). Third, genome stability is a complex trait influenced by hundreds of genes in addition to the genome structure itself and the environment. This has two consequences: 1)first, it may be difficult to identify its complete genetic basis; and 2)second, a certain level of genome instability may be tolerated, until a “threshold” is reached. The best-characterized examples, such as some presented here, have a simple genetic basis, but these may be the exception rather than the rule.

Finally, one may ask whether genome instability is merely one of many types of genetic incompatibility, or is instead a fundamental characteristic of the hybrid genome. We argue that because genomes are highly co-adapted evolutionary units, genome stability can break down at the earliest stages of development following hybridization. As such, genome instability has a central role in consolidating divergence between nascent species. More work in diverse organisms will provide the data to determine the frequency of genome instability in hybrids, to test if it directly contributes to reproductive isolation and speciation, and to address other outstanding questions (Box 1).

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- Genome stability is intimately linked to speciation and evolution.
- Genome stability is a complex trait.
- Genome instability may be a widespread cause of hybrid incompatibility.
- Hybridization can trigger genome instability in multiple ways.

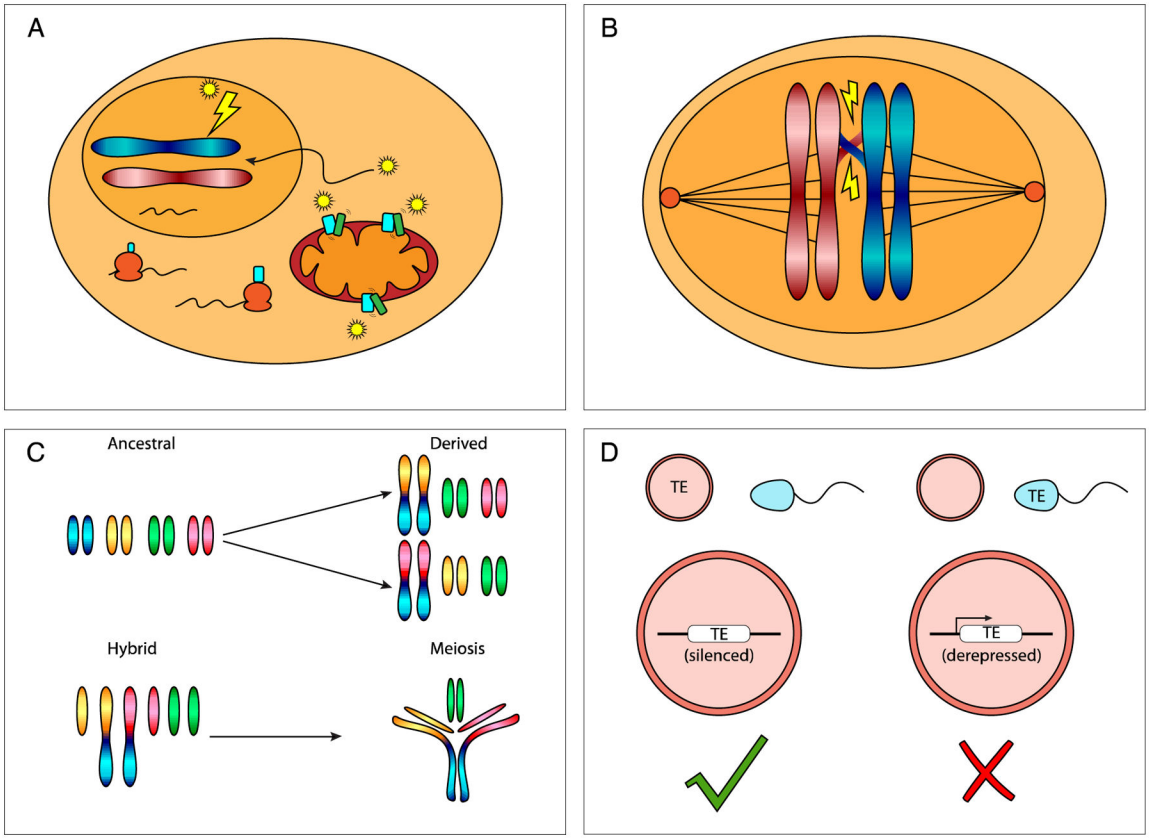

Figure 1. Schematic representation of genome instability mechanisms contributing to post-zygotic reproductive isolation

A. Mito-nuclear incompatibilities may lead to increased reactive oxygen species production. A nucleus-encoded protein (light blue) is incompatible with a mitochondria-encoded protein (green). These two proteins interact together in the electron transport chain in sub-optimal ways due to amino acid changes between two lineages. This leads to inefficient oxidative phosphorylation and release of reactive oxygen species (yellow stars), which causes DNA damage. B. DNA mismatch proteins halt meiotic recombination between divergent sequences (here, between divergent homologous chromosomes in red and blue), reducing fertility of hybrids. C. Different Robertsonian chromosome rearrangements occur between diverging lineages (top panel). Upon secondary contact, these form complex and unstable arrangements during hybrid meiosis, reducing fertility (lower panel). D. Transposable element derepression in hybrids. Diverging lineages carry different transposable elements. Maternally loaded piRNAs initiate transposable element repression, maintaining silencing in the zygote (left panel). Paternally contributed transposable elements may be derepressed if the female fails to load repressive piRNAs. This leads to transposable element mobilization with potentially deleterious consequences for the progeny (right panel).