Cytonuclear Genomic Interactions and Hybrid Breakdown

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Abstract

Reduced fitness in interpopulation hybrids can be a first indication of genetic incompatibilities that may ultimately lead to reproductive isolation and speciation. A growing number of cases of hybrid breakdown have been traced to incompatibilities between the nuclear genome and the organellar genomes of the mitochondria and chloroplasts. Although these organellar genomes derive from ancient bacterial endosymbioses, they have been vastly reduced in size and now encode relatively few genes. The remaining genes are necessary but not sufficient for organelle function. In fact, most proteins functioning in the organelles are encoded in the nuclear genome and need to be imported after synthesis in the cytosol. The necessary interactions between organelle and nuclear genomes have resulted in some degree of coadaptation within all natural populations. Hybridization brings together previously untested allelic combinations and can disrupt intergenomic coadaptation, resulting in organelle dysfunction and, consequently, hybrid breakdown.

1. INTRODUCTION

One approach to understanding how populations or species diverge genetically across their geographic ranges is to examine the phenotypes expressed by hybrids between populations. Whether in nature or in the laboratory, interpopulation hybrids, and especially second-generation (F_2) hybrids, often show reduced fitness compared with the parental lineages. This "hybrid breakdown" of fitness can be viewed as an indicator of an early stage in the evolution of new species, so understanding the molecular basis of the phenomenon may give clues to the genetics of species formation. After all, if each parent population has high fitness, why is hybrid fitness depressed? A widely accepted model for hybrid incompatibility was derived (independently) by Bateson (1909), Dobzhansky (1937), and Muller (1942), known as the BDM model. In short, incompatibilities arise when alleles at different loci that have not been tested together by evolution are forced to interact for the first time in hybrids, resulting in intrinsic selection against some of the new multilocus genotypes. Recently, several studies have reviewed the genes responsible for several cases of hybrid breakdown (e.g., Johnson 2010, Maheshwari & Barbash 2011, Presgraves 2010). Although the number of cases is small, it is tempting to search for a pattern: Are there particular types of genes that are predisposed to causing hybrid incompatibilities? The general conclusion is that patterns are not immediately obvious—a diversity of gene types can be involved in hybrid incompatibility.

Despite this apparent lack of a general pattern across known cases of BDM incompatibilities, recent reviews have noted numerous cases where hybrid breakdown is associated with mitochondrial or chloroplast function (Burke & Arnold 2001, Burton & Barreto 2012, Greiner et al. 2011). Understanding the evolutionary history and cellular functions of these organelles gives some clues as to why they might be involved in hybrid breakdown (e.g., Lane 2011). Unlike other cellular components, mitochondria and chloroplasts are not synthesized de novo by eukaryote cells. Rather, reflecting their evolutionary origin as endosymbiotic bacteria, they are self-replicating and are passed between generations as intact organelles. Remarkably, over the billion plus years of eukaryote evolution, both mitochondria and chloroplasts have retained highly reduced but functional genomes derived from their original bacterial genomes. Despite their small size, these organellar genomes are necessary (but not sufficient!) for cell function and must be replicated and expressed within the organelles themselves; these are processes that involve interactions with large numbers of nuclear gene products. Consequently, animals and plants have two or three different cellular compartments carrying out the processes of DNA replication, transcription, and translation, and each requires extensive intergenomic interaction. Finally, these semiautonomous organelles play essential roles as the powerhouses of eukaryotic cells: The mitochondria are the site of aerobic metabolism, and chloroplasts are where photosynthesis takes place in light-dependent autotrophs. Small perturbations in these functions can potentially have large fitness consequences.

Several features of the structure and evolution of mitochondrial and chloroplast DNA (mtDNA and cpDNA) highlight the degree of coadaptation between organellar and nuclear genomes. For example, both organellar genomes encode some essential subunits of metabolic enzyme complexes (the oxidative phosphorylation, or OXPHOS, system in mitochondria and the photosynthetic apparatus in chloroplasts) and some parts of the protein synthetic machinery required to make those subunits. Remaining enzymatic and structural components of the machinery comprise a large set of imported nuclear gene products. The proteome of metazoan mitochondria, for example, includes over 1,000 proteins, but only 13 of the genes encoding those proteins remain in the mtDNA (Calvo & Mootha 2010). Hence, the function of both organelles is wholly dependent on nuclear-encoded proteins. Genome size and evolution, however, differ greatly between organelles within and among taxa. Animal mitochondrial genomes are small and highly conserved in size

(14–18 kb) and gene content (13 protein coding genes, 2 rRNAs, and 22 tRNAs). With regard to nucleotide substitution rates, animal mtDNA evolves more rapidly than the nuclear genome with few exceptions (e.g., cnidarian, Shearer et al. 2002). Relative rates vary across animal taxa: In *Drosophila*, mtDNA substitution rates are approximately twice those in nuclear DNA; the ratio is over 20-fold in ungulates, and 30–40-fold in primates (Osada & Akashi 2012). Animal mtDNA molecular evolution is restricted to point mutations and indels, because this genome contains no introns and does not recombine.

Land plants may provide even more opportunities for intergenomic incompatibilities than animals because their nuclear genome interacts with chloroplast and mitochondrial products through largely different pathways. Plant chloroplast and mitochondrial genomes encode a comparable number of genes, with 120–140 genes in mtDNA (Schuster & Brennicke 1994) and 87–115 genes in cpDNA (Greiner et al. 2008b, Sato et al. 1999, Sugiura 1989). As mentioned above, these genes encode only a small fraction of the total proteome found in these plant organelles; as many as 3,000 proteins may be targeted to the mitochondria (Millar et al. 2005), whereas analyses of the *Arabidopsis thaliana* chloroplast proteome have identified 1,323 proteins (Bruley et al. 2012). Patterns of genome size, molecular evolution, and inheritance, however, differ greatly between organelles and vary across taxa. Plant mtDNA shows a wide range in size, from 195 kb to over 11,000 kb, maintaining a similar number of genes (Lang et al. 1999, Sloan et al. 2012), whereas cpDNA is more conserved in size across species (170–217 kb; Sugiura 1989). In contrast to the case for animal systems, substitution rates in plant mtDNA are generally ~10–20-fold lower than in respective nuclear DNA (but see Cho et al. 2004 and Sloan et al. 2012), and they are also 3–8-fold lower than rates in cpDNA (Wolfe et al. 1987). Plant mtDNA contains many repeated elements and introns (composing ~90% of the total sequence; Galtier 2011) and undergoes frequent recombination (Palmer & Herbon 1988). In turn, intergenic regions and introns may amount to 45% of cpDNA (Greiner et al. 2008b). Finally, mtDNA inheritance is predominantly maternal in most plants, whereas cpDNA is maternally or biparentally inherited in angiosperms and paternally or biparentally inherited in gymnosperms (Xu 2005). In sum, the functional interdependencies of organellar and nuclear genomes might be expected to lead to more frequent coadaptation compared to systems where all components derive from the nuclear genome.

How can we observe the hypothesized intergenomic coadaptation? Perhaps the most direct evidence for intergenomic coadaptation comes from laboratory experiments that manipulate the organellar composition in vitro, in cells or in whole organisms (**Table 1**). In an early example, King & Attardi (1989) took human cell lines that had been experimentally depleted of mitochondria and repopulated them with mitochondria from other human cell lines, forming hybrid cells or "cybrids." The metabolic activity of the resulting cybrid lines often differed significantly from that of either the original host or mitochondrial donor lines, indicating that metabolic phenotype was a consequence of the interaction between the nuclear and mitochondrial genomes. Many studies have yielded similar results (see Ballard & Melvin 2010). Cybrid approaches in plants have been used to create hybrid cells with different nuclear, mitochondrial, and chloroplast composition and have led to observations of incompatibilities between nuclear and chloroplast genomes. For example, nuclear-encoded RNA editing enzymes from *Atropa belladonna* fail to edit nucleotides in the *atp*A gene located on *Nicotiana tabacum* plastomes, resulting in albino cybrids with reduced photosynthetic ability. The reciprocal cybrid is green (Schmitz-Linneweber et al. 2005), an asymmetry that is consistent with the BDM model (Turelli & Moyle 2007). On the basis of these results, we suggest that hybridization between genetically divergent populations can disrupt intergenomic interactions and result in organelle dysfunction and reduced hybrid fitness.

An alternate approach for establishing the role of cytonuclear interactions on hybrid fitness is based on the different patterns of hereditary transmission of organellar genomes (mostly maternal)

Table 1 Different approaches to study intergenomic interactions and hybrid breakdown

Approach	Evidence	Expectation	Example organisms	References
Bioinformatics	Correlated mutations in functionally interacting proteins	Accelerated rates of evolution in nuclear-encoded proteins interacting with organelles	Copepods	Barreto & Burton 2013
			Fruit flies	
			Parasitoid wasps	
			Yeast	
	Correlated mutations in interacting residues predicted by 3D structure	Codons that show rapid evolution in one protein interact directly with divergent sites on the interacting protein	Primates	Osada & Akashi 2012
Hybridization in the lab	Cytonuclear enzymatic complexes in vitro	Reduced biochemical performance in hybrid protein complexes	Copepods	Ellison & Burton 2006, Rawson & Burton 2002
			Parasitoid wasps	Ellison et al. 2008
			Fruit flies	Sackton et al. 2003
	Cybrids	Reduced metabolic activity in cell lines	Human	King & Attardi 1989
			Tobacco	Schmitz-Linneweber et al. 2005
	Fitness in hybrids	Breakdown in several life-history traits in F_1 or F_2 hybrids	Copepods	Ellison & Burton 2008b
			Fruit flies	Meiklejohn et al. 2013
			Centrarchid fishes	Bolnick et al. 2008
			Seed beetles	Arnqvist et al. 2010
			Monkeyflower	Fishman & Willis 2006
			Sunflower	Levin 2003
			Maize *Brassica* Primroses	Hanson & Bentolila 2004, Stubbe 1964
Hybridization in nature	Natural hybrids	Breakdown in life-history traits in hybrids with mismatched plastids	Bison	Derr et al. 2012
	Hybrid zones	Reduced introgression in organellar genome in a background of high nuclear gene flow	European rabbit	Carneiro et al. 2013
			Killifish	Strand et al. 2012

versus the biparental (Mendelian) inheritance of the nuclear genome. Differences in the fitness of reciprocal hybrid F_1 progeny led Bolnick et al. (2008) to suggest that cytonuclear interactions play a role in reproductive isolation of centrarchid fishes. Also using laboratory crosses, Ellison & Burton (2008a) showed that the reduced fitnesses observed in F_2 and F_3 interpopulation hybrids in the copepod *Tigriopus californicus* could be "rescued" by backcrossing to the maternal (but not paternal) parental population (**Figure 1**). Backcrossing reintroduces a complete (haploid) nuclear genome into the progeny, so that the maternal backcross has a full parental cytonuclear complement, whereas the paternal backcross leads to a mismatch between nuclear and cytoplasmic genomes.

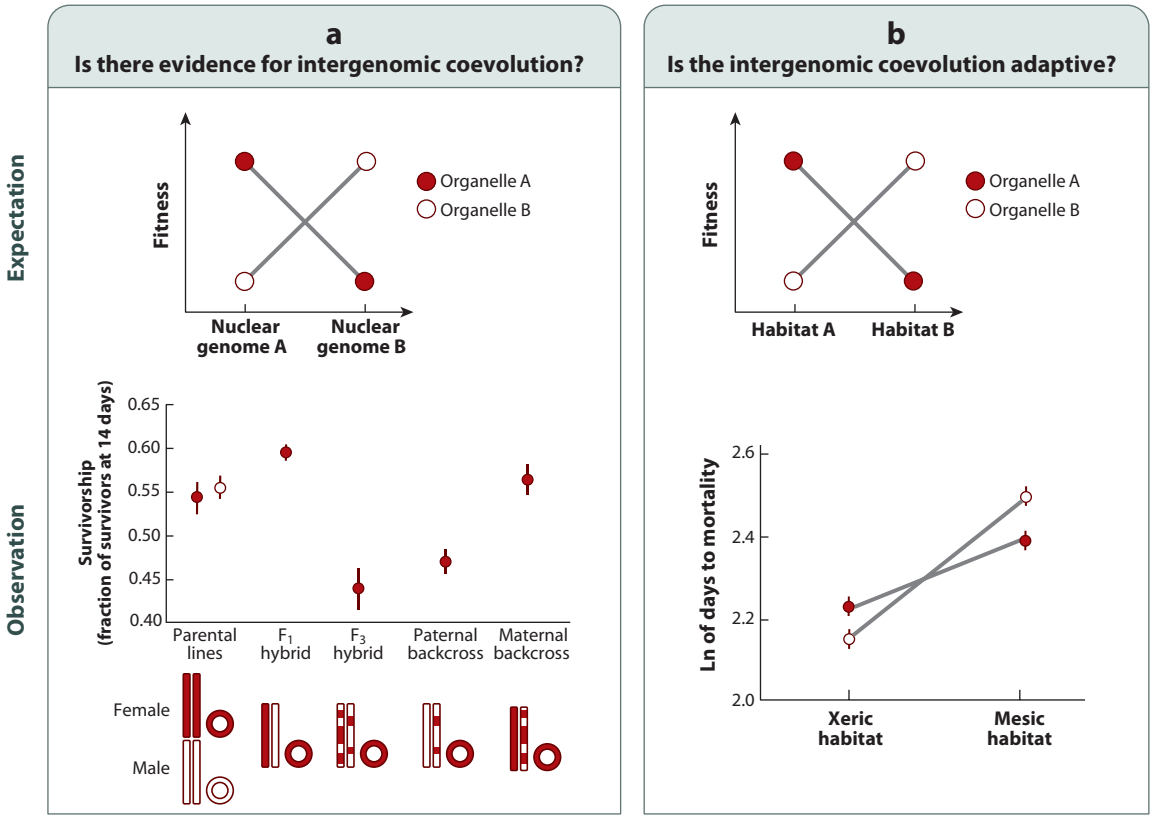

Figure 1

Hypothesis testing for intergenomic coadaptation favored by intrinsic and by extrinsic selection. (*a*) Intrinsic selection provides higher fitness to each organelle in its own nuclear genomic environment. An example is shown using an interpopulation cross between two populations of the marine copepod *Tigriopus californicus*. The data show that hybrid breakdown maps to the mitochondrial genome: Mismatch of mitochondrial and nuclear genomes in F_3 hybrids causes reduced fitness, which is restored in the offspring of maternal backcrosses. Two other interpopulation crosses and all reciprocals show a consistent pattern (Ellison & Burton 2008b). (*b*) Extrinsic selection provides higher fitness to each organelle in its own ecological environment. An example is shown using interspecific crosses of sunflowers and reciprocal transplants into the respective habitats, showing that organelles involved in intrinsic hybrid breakdown were also strongly locally adapted to xeric and mesic habitats (Sambatti et al. 2008). In both examples, fitness for each genotype is represented by mean ± standard error of the mean.

A similar approach has documented negative epistasis between nuclear and plastid genomes in plants. For example, interspecific hybrids in *Oenothera* primroses show a wide range of chloroplast dysfunctions, which is clearly recognized in their pale or bleached leaves (Stubbe 1964). van der Meer (1974) performed a series of backcrosses between hybrids and either parental species and observed that backcrosses that were species-matched for nucleus and plastid restored normal green color and viability.

2. DRIVING FORCES BEHIND INTERGENOMIC COADAPTATION

At least three evolutionary scenarios can lead to coadaptation of nuclear and organellar genomes. Following a brief introduction below, we provide some detailed examples and assess their relative

roles in cases of hybrid breakdown. (*a*) Compensatory coadaptation: Because organellar genomes lack sexual reproduction and have limited recombination, they are susceptible to fixation of mildly deleterious mutations either by genetic drift or by hitchhiking with a favorable mutation sweeping to fixation (genetic draft; e.g., Oliveira et al. 2008); such mutations lead to intrinsic selection favoring compensatory nuclear alleles to regain optimal organelle function (Rand et al. 2004). When interpopulation gene flow is restricted, each population follows a unique coadaptive intergenomic trajectory, and organellar genomes ultimately function best in the presence of their coadapted nuclear genome. (*b*) Adaptive divergence: Some portion of the mutations in organellar genomes may confer adaptive phenotypes in specific environments. These adaptive mutations may be fixed by natural selection and subsequently favor variants in the nuclear genome that are coadapted to an intrinsic genomic environment or that further optimize environmental adaptation. (*c*) Intergenomic conflict: Mutations in organellar genomes can result in their overrepresentation in subsequent generations (as a selfish gene; see Budar et al. 2003, Johnson 2010) while ultimately leading to reduced fitness for the nuclear genome. Selection favors a nuclear mutation that restores a balanced fitness of both genomes. The conflict between genomes is thus resolved by intergenomic coadaptation.

2.1. Compensatory Coadaptation

Intergenomic coadaptation results from interactions between nuclear-encoded proteins and organelle gene products (including proteins and RNAs) and regulatory motifs in the organellar genomes themselves. Because these interactions are typically not known to promote fitness in a specific environment, most appear to be cases of compensatory evolution, where a nuclear gene variant mitigates the consequences of a deleterious organellar mutant (but this has rarely been tested). A few examples are highlighted below (**Table 2**).

2.1.1. Subunit incompatibilities in the mitochondrial OXPHOS system. Because the only proteins encoded in metazoan mtDNA are subunits of the OXPHOS system, mitonuclear protein-protein interactions have been widely studied (e.g., Ballard & Melvin 2010, Blier et al. 2001, Castellana et al. 2011, Rand et al. 2004). A diversity of approaches has provided evidence for the coadaptation of nuclear and mtDNA-encoded OXPHOS subunits. In an especially interesting analysis, Osada & Akashi (2012) found compelling evidence for compensatory evolution in nuclear subunits of OXPHOS complex IV in mammals. First, they found that despite a higher rate of synonymous substitutions in mtDNA versus nucDNA (20–40 fold in mammals), there was no evidence for adaptive evolution in the mtDNA-encoded subunits; in contrast, elevated rates of amino acid substitution were found in nucDNA-encoded subunits specifically in those positions where they interact with variable mtDNA-encoded subunits. Next, using a phylogenetic analysis, Osada & Akashi (2012) were able to infer temporal sequences of evolutionary changes and found that mtDNA changes were followed by nucDNA changes, a pattern that clearly supports the predictions of the compensatory mutation model. This temporal pattern of compensatory mutation has not been widely verified in other systems to date. Azevedo et al. (2009) argue that the compensatory nuclear state may already exist in a population, making the population preadapted to an otherwise deleterious mtDNA mutation. Dowling et al. (2007) observed significant variation in fitness of mtDNA haplotypes when expressed on different nuclear genotypes found within a panmictic population of *Drosophila melanogaster*, a result that supports the notion that compensatory evolution might be based on standing variation versus new mutations.

Outside of model systems, it is often difficult to isolate the specific genes involved in incompatibilities. Rawson & Burton (2002) used in vitro experiments to test for intergenomic coadaptation.

Table 2 Summary of molecular pathways requiring interactions between nuclear-encoded and organelle-encoded products

Organellar function	Dominant interactions	mtDNA-encoded genes	nucDNA-encoded genes	Examples indicating hybrid breakdown
Animals and yeast				
ATP production	Protein-protein	Animal: 13 protein subunits Yeast: 7 protein subunits	Animal: ~75 protein subunits Yeast: ~48 protein subunits	Evolutionary rate of interacting subunits (e.g., Osada & Akashi 2012), functional interactions and fitness consequences (reviewed by Ballard & Melvin 2010)
Transcription	Protein-DNA	Noncoding control regions (promoters and terminators)	Animal: mtRPOL, TFAM, TFB1, TFB2 Yeast: Rpo41, Mtf1	Functional interactions between mtRPOL and mtDNA: human/mouse (Gaspari et al. 2004), copepod populations (Ellison & Burton 2008a).
Replication	Protein-DNA	Noncoding origin of replication	Animal: DNA polymerase, mtRPOL, TFAM, helicase, ligase Yeast: DNA polymerase, Rpo41, helicase, ligase, Mtf1	mtDNA copy number in hybrids (Ellison & Burton 2010)
Translation	Protein-RNA	Animal: 12S and 16S rRNAs Yeast: large and small subunit rRNAs, 1 ribosomal protein, 1 RNase P RNA subunit	Animal: ~80 ribosomal proteins Yeast: ~50 ribosomal proteins, 8 RNase P protein subunits	Translation deficiency in hybrids (Lee et al. 2008), poor intron excision (Chou et al. 2010), ribosomal protein divergence (Barreto & Burton 2013, Matthews et al. 1978)
		Animal: 22 tRNAs Yeast: 24 tRNAs	Animal: 17 aminoacyl tRNA synthases (aaRS), initiation factors, elongation factors Yeast: 19 aaRS	
Plants (mitochondrial functions)				
ATP production	Protein-protein	19 protein subunits	~99 protein subunits	
Transcription	Protein-DNA	16–29 transcription promoters	2 single-subunit RNA polymerases, at least 7 DNA-binding cofactors	
RNA processing	Protein-RNA	Up to 441 mRNA editing sites, 22 introns	PPR proteins (150–450 predicted; at least nine target mitochondria)	Restorer (*Rf*)-of-CMS genes are almost always in the PPR family (e.g., Barr & Fishman 2010; reviewed by Chase 2007)
Replication	Protein-DNA	Noncoding origin of replication	2 gyrases (dual-targeted), 2 DNA polymerases (dual-targeted), 2 proteins for recombination surveillance	

(*Continued*)

Table 2 (*Continued*)

Organellar function	Dominant interactions	mtDNA-encoded genes	nucDNA-encoded genes	Examples indicating hybrid breakdown
Translation	Protein-RNA	8 ribosomal proteins, 3 rRNAs	63 ribosomal proteins	Reciprocal loss of a duplicated nuclear-encoded mitochondrial ribosomal protein causes sterility in rice hybrids (Yamagata et al. 2010)
		18 tRNAs	2 tRNAses, 22 aaRS (all dual-targeted, 17 to mitochondria and chloroplasts, and 5 to mitochondria and cytosol)	
Plants (chloroplast functions)				
Photosynthesis	Protein-protein	~30 subunits	~43 subunits	
Transcription	Protein-DNA	Multiple transcription promoters (>200); multisubunit RNA polymerase (PEP)	Single-subunit RNA polymerase (NEP), up to 6 sigma factors for PEP, multiple transcription factors	Possible loss of PEP and NEP promoters for two photosynthesis genes in *Oenothera* (Greiner et al. 2008)
RNA processing	Protein-RNA	Multiple introns and RNA editing sites	PPR proteins (150–450 predicted; at least 11 target chloroplasts)	Pigment deficiency in cybrids caused by failure to edit *atp*A gene (Schmitz-Linneweber et al. 2005)
Replication	Protein-DNA	Noncoding origin of replication	2 DNA polymerases (dual-targeted), DNA helicases and topoisomerases	
Translation	Protein-RNA	21 ribosomal proteins, 4 rRNAs	51 ribosomal proteins	
		37 tRNAs	17 dual-targeted and 2 unique aaRS	

Abbreviations: CMS, cytoplasmic male sterility; NEP, nuclear-encoded RNA polymerase; PEP, plastid-encoded RNA polymerase; PPR, pentatricopeptide repeat.

The primary result was that CYC (a small nuclear-encoded protein that transfers electrons between OXPHOS complexes III and IV) from a San Diego population was oxidized significantly faster by mitochondria from the San Diego (rather than a Santa Cruz) population; CYC from Santa Cruz showed faster oxidation by Santa Cruz mitochondria, consistent with intergenomic coadaptation. The use of purified CYC in such assays eliminates the possibility that the effects are due to unknown linked loci; however, the degree to which in vitro enzymology is translated to hybrid fitness remains difficult to assess.

2.1.2. Photosynthetic dysfunction. Bleached or variegated phenotypes in interspecific hybrids of many angiosperms have long been recognized as the outcome of plastome-genome incompatibilities (Smith 1954, Stebbins 1950, Stubbe 1964). These phenotypes are associated with reduced photosynthetic capacity, particularly with impaired photosystem II activity (Glick & Sears 1994, Greiner et al. 2008a), and hence are likely to be selected against in nature. However, this phenomenon has not been widely observed (it has been found in only 14 genera of angiosperms; Greiner et al. 2011); the role of plastome-genome incompatibility in hybrid breakdown and speciation has been largely overlooked (Greiner et al. 2011, Levin 2003). Greiner et al. (2011)

argue that this is attributable to detection constraints: The most readily detectable phenotype from plastome-genome incompatibility is hybrid variegation, which requires biparental transmission of plastids (which is found in only one-third of angiosperms; Birky 2001). Hence, other phenotypes caused by plastome-genome epistasis may often go unnoticed. Conversely, it is not surprising that the best-described cases of plastome-genome incompatibility come from species with biparental plastid inheritance. In fewer yet no less important cases, sterility of hybrid progeny seems to also be dependent on plastome-genome combinations (Bogdanova & Berdnikov 2001, Stubbe & Steiner 1999).

Patterns of plastome-genome incompatibility have been widely reported from crop and ornamental plant taxa. Reciprocal differences in chlorophyll deficiency were observed in interspecific hybrids in *Acacia* trees (Moffett 1965) and sweetclover (*Melilotus* spp.; Smith 1954). More recently, genetic markers have been useful in assessing the direction of incompatibility by permitting identification of parent-of-origin of chloroplasts from hybrid tissues. Kita et al. (2005) analyzed plastid DNA in progenies from the reciprocal crosses between *Menziesia* × *Rhododendron* and demonstrated that all green seedlings harbored the *Menziesia* cpDNA, whereas albino and pale-green progenies contained *Rhododendron* cpDNA. A similar asymmetry was observed in interspecific crosses within *Rhododendron* (Michishita et al. 2002). Moreover, cpDNA identification in different tissues of the same individual exhibiting pigment variegation provides additional support for the occurrence of plastome-genome epistasis (Metzlaff et al. 1982).

The relevance of plastome-genome incompatibility in plant speciation has become evident from detailed genetic studies in the genus *Oenothera* (Stubbe 1989). In this group, three basic nuclear haploid genomes (denoted A, B, and C) are associated with five distinct plastid haplotypes (denoted I–V). Of the 30 possible plastome-genome combinations, only 12 produce normal green phenotypes; the remaining combinations result in a wide range of chloroplast dysfunctions, from highly reduced photosynthetic capacity to embryo lethality (Stubbe 1964). Many of these incompatible combinations serve as strong barriers to hybridization in nature. For instance, laboratory hybrids among wild stocks of *Oenothera elata* (genotype AA-I), *Oenothera grandiflora* (BB-III), and *Oenothera argillicola* (CC-V) exhibit strong chloroplast inviability in 5 of the 6 possible interspecific crosses (Greiner et al. 2011, Stubbe 1989). No other form of pre- or postzygotic isolation is known to separate these species. In *Oenothera* species with overlapping ranges (e.g., *Oenothera nutans*, *O. argillicola*, and *Oenothera parviflora*), most interspecific hybrids are inviable owing to chloroplast dysfunction. Prezygotic barriers in the form of floral and mating system differences have already evolved in these areas of overlap (Dietrich et al. 1997), suggesting hybrid breakdown caused by plastome-genome incompatibilities has served as a strong barrier to reproduction.

Despite well-described patterns of hybrid breakdown in photosynthetic capacity, the genetic mechanisms underlying plastome-genome incompatibilities are largely unknown. Greiner et al. (2008a) used a bioinformatic approach to compare the five *Oenothera* plastome sequences and to search for genomic differences that are consistent with the 30 hybrid phenotypes (described above). The authors proposed that an intergenic deletion between *clp*P and *psb*B genes (involved in photosystem II) in plastome type I explains the lower photosynthetic capacity of hybrids harboring that plastome. The nuclear components of the incompatibility, however, have not been elucidated. In contrast, Bogdanova et al. (2009) mapped photosynthetic dysfunctions in hybrids between wild and cultivated subspecies of *Pisum* peas to two unlinked nuclear loci, but the specific cpDNA loci involved were not identified.

2.1.3. Transmission and expression of organellar genomes. In addition to coding for some key metabolic functions, organellar genomes must regulate their own replication, transcription, and

translation. Consequently, these processes occur separately in up to three cellular compartments simultaneously with component parts encoded in the multiple genomes.

2.1.3.1. Mitochondrial DNA replication. Replication of mtDNA requires a different set of proteins than those required for the replication of the nuclear genome. These genes are encoded in the nuclear genome and include DNA polymerase γ, an accessory subunit p55, and replication factors, such as the mitochondrial single-stranded DNA binding protein and the mtDNA helicase. Mitochondrial RNA polymerase (mtRPOL) plays key roles in both mtDNA replication and mtDNA transcription. In the former, mtRPOL synthesizes the RNA primer that is required for polymerase γ–mediated DNA replication. Ellison & Burton (2010) examined mtDNA copy number and transcription in laboratory hybrids between divergent populations of the copepod *T. californicus*. Lines having different combinations of mtRPOL and mtDNA showed a genotype-dependent negative association between mitochondrial transcriptional response (see below) and mtDNA copy number. The authors hypothesize that an observed increase in mtDNA copy number and reduced mtDNA transcription in hybrids reflects the regulatory role of mtRPOL; depending on the mitonuclear genotype of mtRPOL, hybridization may disrupt the normal balance between transcription and replication of the mitochondrial genome.

2.1.3.2. Hybrid breakdown in transcription of organellar genomes. Expression of the proteins encoded on organellar genomes requires transcriptional machinery that is mostly encoded in the nucleus; a single multisubunit RNA polymerase gene has been retained in chloroplast genomes. Although we are not aware of studies focusing on the activity of specific plastome transcription components in hybrids, a few studies suggest that plastid gene regulation may be involved in plant hybrid breakdown. For instance, Yao & Cohen (2000) showed that mRNA levels of three cpDNA-encoded genes were severely reduced in albino leaf sectors when compared with levels in green leaf sectors of variegated hybrids of *Zantedeschia aethiopica* × *Zantedeschia odorata*. Also, as mentioned above, Greiner et al. (2008a) proposed that impaired transcription of *clp*P and *psb*B photosynthesis genes, owing to deletions of RNA polymerase promoters, is likely responsible for plastome-genome incompatibilities in some crosses within *Oenothera*.

An interesting mitochondrial metabolic phenotype has been observed in multiple cases of hybrid breakdown: OXPHOS enzyme complexes I, III, IV, and V all show reduced activity, whereas complex II is unaffected. Because the former complexes require mtDNA-encoded subunits and complex II does not, this pattern is consistent with a hypothesis that mtDNA is not being efficiently transcribed or translated in hybrids. Ellison & Burton (2006) found this pattern in recombinant inbred lines of *T. californicus* (also see Meiklejohn et al. 2013, discussed below), and Ellison & Burton (2008b) tested the hypothesis that the reductions of OXPHOS enzyme activities were due to depressed mtDNA gene expression. Work on mammalian systems reconstructed in vitro found that a three-component system (mtRPOL and two transcription factors) was required for transcriptional activity and that mouse and human systems were unable to initiate transcription from the heterologous promoter (Gaspari et al. 2004). Ellison & Burton (2008a) predicted that hybrid lines with mtRPOL and mtDNA from the same natural population would not have depressed transcription because the mtRPOL would be coadapted to the mtDNA binding site (promoter). In contrast, hybrid lines with mismatched mtRPOL and mtDNA would show reduced transcription. Quantitative PCR assays showed that only expression of mtDNA-encoded genes (not nuclear genes) differed among hybrid versus parental lines. Transcriptional profiles depended on the specific interpopulation cross and were correlated with viability effects; lines homozygous for the mtRPOL allele derived from the same population as the mtDNA generally showed higher mtDNA transcription and higher fitness than mismatched genotype. The strong

effect of mtDNA on mtRPOL genotypic fitness is consistent with the hypothesis that disruption of the mitochondrial transcription in interpopulation hybrids may play a central role in hybrid breakdown.

2.1.3.3. Hybrid breakdown in organellar translation. Although DNA replication and transcription require many different gene products, neither is quite as complex as translation, which requires the assembly of ribosomes and the function of tRNAs in each compartment. Organellar ribosomes are complex structures consisting of two or three structural rRNAs (typically encoded in the organellar genome) and 60 or more ribosomal proteins (RPs) (mostly encoded in the nuclear genome). In metazoans, all RPs are encoded in the nucleus, and a specific set of RPs are targeted to mitochondria. In plants, at least 14 mitochondrial RPs (mRPs) are encoded in the mtDNA (Kubo & Newton 2008, Schuster & Brennicke 1994), whereas the remaining 45–50 are imported nuclear products. Similarly, approximately 20 chloroplast RPs are encoded by the cpDNA, complementing the 40–50 nuclear-encoded RPs targeted to the plastid (Greiner et al. 2008b, Sugiura 1989). Intergenomic coadaptation predicts that structural changes in organelle-encoded components of ribosomes (e.g., rRNA) create strong selection for compensatory mutations in nuclear-encoded interactants (Burton & Barreto 2012, Rand et al. 2004). Consistent with this hypothesis, Barreto & Burton (2013) found evidence in diverse taxa that elevated rates of mitochondrial rRNA evolution (over nuclear rRNAs) result in elevated rates of evolution in mRPs relative to RPs interacting with the slower evolving nuclear rRNAs.

Outcrossing between taxa with high divergence in mitochondrial ribosomal components might be expected to result in hybrids with dysfunctional mtDNA translation machinery. Although direct experimental evidence for ribosomal dysfunction in hybrids is still lacking, some studies appear to show disruption of organelle genome translation. Yamagata et al. (2010) worked with F_1 hybrids between cultivated rice (*Oryza sativa*) and a wild relative (*Oryza glumaepatula*); F_1 hybrids with *O. sativa* cytoplasms exhibit complete pollen sterility. Fine-scale mapping of pollen sterility in recombinant lines of the above cross showed that reciprocal loss of a duplicated nuclear-encoded mRP (*mRPL27*) is tightly associated with pollen mitochondrial formation and development. This illustrates how loss-of-function alleles, owing to duplication and loss of loci within a lineage, may rapidly create intergenomic incompatibilities and postzygotic barriers.

Animal mitochondrial genomes typically encode a set of 22 tRNAs that are sufficient for translation, although there are confirmed cases of nuclear tRNAs being imported into the mitochondria (Schneider 2011). The situation is more complex in plants, where some tRNA genes have been horizontally transferred to the mtDNA, and functional tRNAs are frequently imported from the nucleus (Joyce & Gray 1989, Maréchal-Drouard et al. 1988). However, regardless of the tRNA origin, the aminoacylation step (charging the tRNA with the appropriate amino acid) is catalyzed by a nuclear-encoded tRNA synthetase (aaRS). These aaRS genes produce enzymes that function in the cytosol, the mitochondria or the chloroplast, or some set of the three compartments. Consequently, different constraints act on different aaRS genes, as some need only recognize an mtDNA-derived tRNA, whereas others must function with two or even three different tRNAs in multiple cellular compartments (Duchene et al. 2009).

Because the function of tRNAs is highly dependent on secondary structure, mutations in aaRS genes result in a diversity of functional deficiencies (including a range of human diseases; see, e.g., Scaglia & Wong 2008). Here we are interested in the interactions between organellar tRNAs and the nuclear-encoded aaRS. For example, Moreno-Loshuertos et al. (2011) found that single nucleotide substitution in the anticodon loop of the mitochondrial $tRNA^{Ile}$ results in reduced OXPHOS capacity in mouse cell lines. The tRNA mutation appears to result in inefficient aminoacylation—i.e., the $tRNA^{Ile}$ fails to get charged; this results in reduced translation

of mtDNA-encoded OXPHOS subunits. Differentiation in mitochondrial tRNAs among populations is well documented; for example, a 460-bp region encoding six contiguous tRNAs in *T. californicus* shows a 10% sequence divergence between populations (Burton et al. 2007). If coadaptation occurs in natural populations, hybrids might be expected to experience some level of dysfunction in mitochondrial translation owing to mismatches between mtDNA-encoded tRNAs and their associated nuclear-encoded aaRS genes.

Such a case has recently been demonstrated. In a particularly elegant study, Meiklejohn et al. (2013) identified the molecular basis of a tRNA/aaRS interaction that leads to fitness loss in hybrids between *D. melanogaster* and *Drosophila simulans*. An amino acid polymorphism in the *D. melanogaster* nuclear-encoded mitochondrial tyrosyl-tRNA synthetase interacts epistatically with a polymorphism in the *D. simulans* mitochondrial-encoded $tRNA^{Tyr}$ to significantly delay development and decrease fecundity. The incompatible genotype specifically decreases the activities of OXPHOS complexes I, III, and IV that contain mitochondrial-encoded subunits, indicating that mitochondrial transcription or translation is affected by this interaction; given the genes involved, translational deficiency would be the most likely cause. Most important, the identification of the putative causal mutations was verified by transgenic technology. These findings show a clear example of disruption of coadaptation between mitochondrial tRNAs and the nuclear-encoded aaRS.

Intergenomic incompatibilities in mtDNA translation are well characterized in hybrids of *Saccharomyces*. In this group, the mitochondrial genome is larger than that of animals (~71 kb) and contains several introns and large intergenic regions (Procházka et al. 2012). This genome encodes only 8 proteins and 27 RNAs, so most of the ~750 proteins functioning in the mitochondria (Sickmann et al. 2003) are imported from the cytosol. In the laboratory, thousands of loci can be screened individually for their capacity to rescue metabolic fitness in low-viability hybrids, permitting precise dissection of molecular mechanisms (Chou & Leu 2010). Lee et al. (2008) detected that the mitochondrial-targeting *AEP2* gene, encoded in the nucleus, rescued spore viability in hybrids of *Saccharomyces bayanus* (Sb) × *Saccharomyces cerevisiae* (Sc), which harbored Sc mitochondria. The function of the Aep2 protein is to facilitate the translation of the mtDNA-encoded *OLI1* gene by processing its 5′-UTR. After reporting high divergence in the *OLI1* 5′-UTR sequence between *S. cerevisiae* and *S. bayanus*, the authors proposed that, owing to coadaptation of Sb-Aep2 with native Sb-*OLI1*, Sb-Aep2 malfunctions during translation of the heterospecific Sc-*OLI1*. Indeed, Sb × Sc hybrids failed to produce Oli1 product (Lee et al. 2008).

When yeast hybrids involving *S. cerevisiae* contained *S. bayanus* or *Saccharomyces paradoxus* (Sp) mitochondria, strong sterility occurred at the F_2 stage. Hybrid rescue screening again revealed a nuclear-encoded mitochondrial protein (Mrs1) as a major component of hybrid breakdown. Functional assays revealed that hybrids of both crosses lacked mature mRNAs for the mtDNA-encoded *COXI* gene. Functionally, Mrs1 participates in excision of *COXI* introns in all three species. *COXI* in *S. cerevisiae*, however, differs from that of the other two species by having one instead of two introns. Incompatibility between Sc-*MRS1* and Sb- and Sp-*COXI* mRNAs hence likely occurs because Sc-Mrs1 coevolved to excise only one *COXI* intron (Chou et al. 2010).

2.2. Adaptive Divergence

In general, the interactions between the organellar genome and nuclear genes products occur within a cellular environment that may be largely independent of the ecological environment and evolve in response to intrinsic natural selection. However, if one of these units (nuclear or organellar) is additionally locally adapted to a specific ecological environment, the effect of extrinsic selection (in addition to intrinsic selection) is expected to affect all the coevolving units.

Organellar genomes play a central role in several metabolic functions that might directly impact an organism's adaptation to its local environment. Where organellar genomes confer adaptation to different environments, extrinsic selection will favor intergenomic coadaptation. Although this process might be quite important in nature, demonstrating the role of extrinsic selection on intergenomic incompatibilities is challenging because it requires testing the fitness of alternative organelles in different genomic and ecological environments (**Figure 1**).

Perhaps the clearest example addressing the role of extrinsic selection on intergenomic incompatibility comes from experimental studies in sunflowers. The replacement of the common sunflower's (*Helianthus annuus*) cytoplasm by the cytoplasms of closely related species (*Helianthus petiolaris*, *Helianthus mollis*, *Helianthus maximiliani*, *Helianthus divaricatus*, *Helianthus angustifolius*, or *Helianthus grosseserratus*) results in plant weakness, delayed maturity, reduced seed weight and pollen inviability (Levin 2003), suggesting that cytonuclear incompatibilities may play a role in establishing reproductive isolation among these congeners. Adaptation to different ecological environments is known to be a major process of diversification in sunflowers (Rieseberg 2006, Rieseberg et al. 2003), and such diversification might lead to environment-specific intergenomic coadaptation. Using reciprocal transplants with controlled crosses, Sambatti et al. (2008) showed that the cytoplasmic genomes of two of these species (*H. annuus* and *H. petiolaris*) are differentially adapted to alternative ecologic environments (mesic versus xeric). Using experimental crosses with all possible combinations of nuclear and cytoplasmic genomes, Sambatti et al. (2008) showed that the cytoplasms of *H. annuus* and *H. petiolaris* show significantly increased survivorship in mesic and xeric habitats, respectively (**Figure 1**).

In animals, several studies show that intergenomic mismatches lead to disruption in ATP production (Ellison & Burton 2006, Meiklejohn et al. 2013), but few studies test whether these interactions are also affected by extrinsic selective regimes. Arnqvist et al. (2010) created experimental interpopulation hybrids in the seed beetle, *Callosobruchus maculatus*, with fully introgressed cytotypes into foreign nuclear genetic backgrounds, and assayed their metabolic rates under two different temperature regimes. Although the direct interaction between mitochondrial and nuclear DNA did not result in significant fitness loss, significant breakdown in metabolic rate was explained by the three-way mitochondrial × nuclear × environment interaction. Their result suggests that some of the hybrid breakdown caused by intergenomic interactions might only be revealed when measured under multiple ecological environments.

Together, these results imply that, in addition to intrinsic intergenomic incompatibilities, extrinsic selection could limit the introgression of organellar genomes and coevolving nuclear alleles in hybrid zones. In such cases, intergenomic interactions may play a significant role in maintaining stable genetic boundaries between incipient species across environmental clines.

2.3. Intergenomic Conflict

Intergenomic conflict occurs as a result of differences in inheritance patterns between nuclear genes (biparental inheritance) and organelle genomes (generally maternal, but biparental in some plants). A dramatic example involves the evolution of cytoplasmic male sterility (CMS) in plants (Budar et al. 2003, Chase 2007). Because males do not pass their mtDNA to offspring, "selfish" mitochondrial variants that can increase the proportion of female offspring, by causing sterility of male flower parts, will increase their frequency in a population. Nuclear genes in turn coevolve to gain increased transmission by restoring male fertility in a CMS-affected lineage. In contrast to metazoan mtDNA, angiosperm mtDNA generally exhibits very low nucleotide substitution rates (Wolfe et al. 1987, but see Cho et al. 2004 and Sloan et al. 2012), but undergoes frequent

recombination and enormous size changes (Palmer & Herbon 1988, Sloan et al. 2012). Mapping studies have revealed that CMS phenotypes, characterized by the lack of pollen or anthers, are frequently associated with the expression of chimeric open reading frames (ORFs) formed through mitochondrial recombination. Interestingly, expression of such chimeric ORFs rarely affects proper respiratory function, so CMS-affected hybrids are otherwise healthy (Hanson & Bentolila 2004, Linke & Borner 2005). The effects of CMS ORFs can be suppressed or counteracted by the product of restorer-of-fertility (*Rf*) genes from the nucleus (Hanson & Bentolila 2004). Hence, a CMS/*Rf*-carrying plant has restored hermaphroditism. Although CMS ORFs can result from a wide variety of chimeric structures, nearly all *Rf* alleles characterized to date belong to the pentatricopeptide repeat (PPR) protein family (Wise & Pring 2002). Functional assays suggest that *Rf* genes function in transcription regulation and RNA editing; male function is restored by either reduction in expression or truncation of CMS-causing transcripts (Lurin et al. 2004, Wise & Pring 2002).

The widespread occurrence of maternally inherited hybrid male sterility suggests that CMS genes are likely more common than currently reported (Chase 2007, Levin 2003, Tiffin et al. 2001). Hermaphroditic individuals carrying CMS/*Rf* alleles are often phenotypically indistinguishable from individuals not carrying these alleles, and hence the CMS phenotype is only revealed in interspecific crosses in which the seed parent (i.e., the mother) has the CMS gene and the pollen parent does not carry a compatible *Rf* allele. The general importance of CMS/*Rf* interactions in creating reproductive barriers is still debated (Rieseberg & Blackman 2010), with most observations made from crop plants (Chase 2007). Studies in monkeyflowers (*Mimulus* spp.), however, provide a valuable example of how mitonuclear interactions may generate hybrid breakdown in plants. Hybrids between *Mimulus guttatus* and *Mimulus nasutus* are often found in areas of sympatry (Vickery 1978), and hybrid male sterility is strongly asymmetric, with *M. nasutus* nuclear genomes being incompatible with *M. guttatus* cytoplasm (Sweigart et al. 2006). As predicted from other cytonuclear incompatibility systems, backcrossing low-fertility hybrids with pollen from the maternal line partially recovers fertility (Sweigart et al. 2006). Genomic mapping in *M. guttatus* characterized a CMS-causing rearrangement of the mitochondrial gene *NAD6* (Case & Willis 2008) and two nuclear PPR proteins capable of restoring fertility (Barr & Fishman 2010). Moreover, the CMS ORF in *M. guttatus* is fixed in a small population but nearly nonexistent in other populations (Case & Willis 2008), providing the opportunity for interpopulation hybrid sterility via breakdown of CMS/*Rf* coadaptation. The presence of a hybrid zone as well as of intraspecific polymorphism in CMS/*Rf* equilibrium makes this system an excellent model for assessing the potential of intergenomic conflicts in generating reproductive barriers.

3. PHENOTYPIC CONSEQUENCES OF INTROGRESSION OF ORGANELLAR GENOMES IN NATURAL INTERPOPULATION

There are a large number of cases in the literature where hybridization among natural populations has resulted in introgression of mtDNA (Toews & Brelsford 2012). Some reports indicate direct phenotypic evidence of hybrid breakdown due to intergenomic interactions, whereas in others evidence for such breakdown can only be inferred from the patterns of introgression.

Before examining cases where introgression of organellar genomes has resulted in hybrid breakdown, it is worth noting that a number of studies show little or no evidence for coadaptation playing a role in interspecific incompatibilities (e.g., Montooth et al. 2010). Indeed, there are numerous cases where mtDNA has introgressed across species boundaries (e.g., Berthier et al. 2006, Doiron et al. 2002, Hofman et al. 2012, Nevado et al. 2011), suggesting that intergenomic coadaptation is not sufficiently strong to create interspecific incompatibilities. The simplest explanation for

these observations, of course, is that coadaptation has not evolved, perhaps owing to either insufficient time in allopatry or lack of relevant genetic variation. However, an alternate explanation is that coadaptation does in fact exist and the required nuclear alleles have cointrogressed with the organellar genome. Such nuclear introgression may not be detected in typical introgression studies that only survey a relatively small number of randomly selected nuclear markers. Fortunately, new methods employing next-generation sequencing approaches may soon resolve this issue.

In a recent study, Derr et al. (2012) report on hybridization between American plains bison (*Bison bison bison*) and domestic cattle (*Bos taurus*). Bison populations were dramatically reduced in size and geographic range owing to hunting in the 1800s and have shown some recovery over the past 100 years. Genetic examination has shown that many modern bison herds contain some introgressed cattle DNA, particularly mtDNA. The weight and height of bison with cattle or bison mtDNA were compared in animals from two different environments: Santa Catalina Island, California (USA), a nutritionally stressful environment, and feedlots in Montana, a nutritionally rich environment. Bison with introgressed cattle mtDNA had lower weight than bison with native mtDNA in both environments, suggesting that the mitonuclear mismatched genotype might be at a competitive disadvantage. Because the same pattern was observed in both environments, the hybrid breakdown was likely due to intrinsic factors.

Although the bison intergenomic hybrids exhibit distinct phenotypes, most cases of hybrid breakdown are reflected in reduced fertility and/or viability and thus hybrid breakdown might be difficult to document in nature. In these cases, rather than take direct measurements of phenotypes, heterogeneous patterns of introgression among genetic markers may provide indirect evidence for hybrid breakdown. In areas of secondary contact between closely related taxa (i.e., hybrid zones), hybridization can disrupt coadapted genetic combinations that evolved in allopatry. Population genetics theory (Barton 1979, Barton & Hewitt 1985) predicts that the spatial distribution of alleles across hybrid zones (clines) will vary based on the fitness the alleles confer to different recombinant individuals or hybrids. Alleles that are equally fit in both genomic backgrounds introgress neutrally as a function of the time since secondary contact and produce smooth transitions in allele frequencies. In contrast, genes involved in genetic incompatibility or local adaptation will show steep transitions in allele frequencies because mismatched genotypes are eliminated by intrinsic or extrinsic selection. Similar to other BDM incompatibilities, intergenomic incompatibilities are expected to result in steep clines in both organellar genomes and in interacting nuclear genes while most of the nuclear genome becomes admixed.

Recent studies in the European rabbit hybrid zone illustrate how heterogeneous patterns of introgression among loci can provide insights into the genetic barriers at early stages of speciation. Some 1.8 Mya, allopatric divergence gave rise to two subspecies that, after the last glacial maximum (~18,000 years ago), established secondary contact in the central Iberian Peninsula (Carneiro et al. 2009). Current patterns of genetic differentiation suggest that high rates of gene flow resulted in genome-wide introgression. Although some loci show introgression throughout the range of both parental populations, a few loci show exceptional steep transitions at the center of the hybrid zone, consistent with high levels of selection against hybrids (Carneiro et al. 2013). Among these loci presumably involved in BDM incompatibilities is the mitochondrial genome. Similar results in killifish (Strand et al. 2012) are consistent with the hypothesis that cytonuclear incompatibilities have evolved at early stages of population divergence and contribute to a barrier to gene flow between populations. However, experimental data are required to distinguish this hypothesis from demographic effects affecting the mitochondria.

Although the value of natural hybrid zones for identifying loci underlying reproductive isolation was recognized decades ago (Barton & Hewitt 1985, Harrison 1993), recent advances in sequencing

technology (noted above) have great potential for genome-wide analyses of introgression in model and nonmodel organisms. Such work will provide important insights into the role of intergenomic incompatibilities in establishing genetic barriers between incipient species.

4. GENOME-LEVEL STUDIES

The remarkable advances in DNA sequencing technologies over the past several years are already revolutionizing the manner in which we can approach the complexities of intergenomic interactions and incompatibilities. Although understanding the physiological and fitness consequences of genetic variation continues to require a diversity of approaches, genome and transcriptome sequencing can efficiently scan the entire genome for patterns of diversity and differentiation, greatly facilitating hypothesis testing and the identification of candidate genes for further analyses. For example, Werren et al. (2010) compared the genomes of three wasp species (genus *Nasonia*) and found that nuclear genes interacting with the mitochondria have elevated rates of evolution. Because intergenomic incompatibilities were previously detected among these species, the genomic data point to specific candidate genes for further analysis.

For most systems, full genome sequences are not yet available. In such nonmodel systems, transcriptome sequencing (sequencing of the mRNA pool isolated from a sample) offers a powerful, yet accessible, approach. By focusing sequencing efforts only on transcribed regions of the genome, sample complexity is greatly reduced and good coverage of the sample can be achieved at reasonable cost. Perhaps more important here is the fact that biological function can be assigned to a substantial portion of the sequences through automated annotation pipelines such as BLAST2GO (**http://www.blast2go.com**). Because the data represent a snapshot of the RNA pool, they provide information on both sequence variation (single nucleotide polymorphisms or SNPs) as well as gene expression. Although few studies provide evidence for direct effects of intergenomic incompatibility on transcription (e.g., Ellison & Burton 2008b), current transcriptome analyses offer a promising approach; for example, such data permit examination of allele-specific differences in transcription, which could be one mechanism by which heterozygous hybrids could mitigate intergenomic incompatibilities (He et al. 2012, Regneri & Schartl 2012).

Transcriptome data can be used to survey all transcribed genes for elevated rates of evolution in a manner similar to the whole genome approach mentioned above (Werren et al. 2010). For example, Gagnaire et al. (2012) used transcriptome sequencing to identify genes with elevated rates of evolution (i.e., high nonsynonymous divergence) between hybridizing European and American *Anguilla* eel species. Remarkably, among 87 nuclear genes found to have high levels of divergence, genes involved in ATP biosynthetic processes were significantly overrepresented. The highest d*N*/d*S* was for the gene *atp5c1*, encoding a key protein that interacts with the mtDNA-encoded ATP synthase 6 in the OXPHOS complex V. The authors conclude that intergenomic incompatibility between taxa at these genes might disrupt normal ATP synthase function in hybrids and contribute to partial reproductive isolation.

In addition to determining rates of evolution in protein coding sequences, transcriptome studies can be used to examine the extent of population differentiation within species. Pante et al. (2012) employed transcriptome sequencing to identify 17,000 SNPs among three disjunct populations of the bivalve *Macoma balthica*, a species where hybrid zones are known to form between divergent lineages. Divergence among the populations was calculated for each SNP using standard F_{ST} statistics, and outlier loci (i.e., differentiation higher than can be explained by random drift) were examined for gene function. The study found that most SNPs in mtDNA genes showed high F_{ST}, consistent with many studies showing elevated population structure for mtDNA. More notable was the observation that among nuclear genes, those with outlier F_{ST} values included several

components of the OXPHOS complexes, especially subunits of the ATP synthase. The authors conclude that the transcriptome scan had revealed evidence of disequilibrium between nuclear and mitochondrial genes and provided suggestive evidence for intergenomic BDM incompatibilities. Again, this study exemplifies the remarkable power of this approach in identifying potential targets of intergenomic selection in natural interpopulation hybrids.

SUMMARY POINTS

1. Reflecting their evolutionary origin as endosymbiotic bacteria, mitochondria and chloroplasts retain small genomes that are necessary but not sufficient for organelle function; consequently cell function is completely dependent on intergenomic interactions.
2. Given organelles' role as the powerhouses of eukaryotic cells, even small disruptions of organellar function can significantly impact fitness.
3. A broad range of interactions occur between genomes, including not only those between protein subunits in enzyme complexes, but also protein/RNA and protein/DNA interactions required for the replication, transcription, and translation of organellar genomes.
4. Hybridization between populations exposes incompatibilities by generating mismatches between nuclear and organellar gene loci that have coevolved in allopatry. Decreased hybrid fitness is then a consequence of impaired organellar functions, such as lowered ATP production or photosynthetic capacity.
5. Intergenomic incompatibilities can result from the disruption of compensatory or adaptive interactions, or disruption of systems that evolved to suppress intergenomic conflict.
6. Intergenomic incompatibilities may play an important role in hybrid breakdown throughout the tree of life (animals, plants, fungi) and generate barriers to gene flow at the early stages of species formation.

FUTURE ISSUES

1. Application of new genome and transcriptome sequencing methods have great promise for resolving questions regarding the extent of intergenomic coadaptation, such as how many and what types of loci are involved.
2. Similar approaches can be used to directly test hypotheses regarding introgression of organellar genomes across natural hybrid zones (i.e., tests of cointrogression of nuclear and organellar genomes).
3. The relative roles of compensatory, adaptive, and genomic conflict interactions remain unclear, and future experimental work is needed to explicitly test the contributions of these different evolutionary scenarios.
4. Much of the current work addressing intergenomic interactions has been concentrated in laboratory experiments. Extending those experiments to natural populations will provide insights into how intergenomic incompatibilities provide sufficiently strong barriers to gene flow to maintain divergence in nature and how these intrinsic mechanisms can facilitate further adaptive divergence to extrinsic ecological environments.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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