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Molecular evolution and genetics of postzygotic reproductive isolation in plants

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Abstract

In just the last few years, plant geneticists have made tremendous progress in identifying the molecular genetic basis of postzygotic reproductive isolation. With more than a dozen genes now cloned, it is clear that plant hybrid incompatibilities usually evolve via two or more mutational steps, as is predicted by the Dobzhansky-Muller model. There is evidence that natural selection or random genetic drift can be responsible for these incompatibilities.

Introduction

The goal of explaining the origin of species has inspired more than two centuries of scientific inquiry, involving early naturalists through to modern evolutionary biologists. Though only hinted at by Darwin [1], the idea that the evolution of reproductive isolation is central to the process of speciation [2] is now widely recognized [3-5]. Reproductive isolating mechanisms that restrict gene exchange between diverging species include prezygotic barriers that limit the potential for mating or zygote formation (e.g. habitat and flowering time differences or pollen-pistil incompatibilities) and postzygotic barriers that reduce the viability or fertility of hybrid offspring if interbreeding does occur. Whereas the evolution of prezygotic isolation is often easily understood as a byproduct of differential adaptation to variable ecological conditions or of selection to reduce the production of low-fitness hybrids, the evolution of postzygotic isolation has been a long-standing mystery [1] because the production of dead or sterile hybrids cannot be favored by natural selection.

The Dobzhansky-Muller model

Dobzhansky [6] and Muller [7] outlined a solution to this puzzle, explaining that if postzygotic isolation is caused by incompatible gene interactions between diverging species then natural selection need not oppose its evolution. A new mutation might function perfectly well in the context of its native genetic background, increasing in frequency until it becomes fixed within the species. But because the fitness of this new variant has only been "tested" against its own genetic background, it might be functionally incompatible with divergent alleles present in foreign genetic backgrounds, resulting in hybrid sterility or inviability. The key insight of the so-called Dobzhansky-Muller model is that, if hybrid incompatibilities are caused by two or more mutational differences between species, there can be transitional genotypes that are adaptive or neutral in ancestral populations and, therefore, not eliminated by natural selection. In contrast, if reduced hybrid fitness is caused by a single mutational step (resulting in heterozygote disadvantage), natural selection is expected to impede the *initial* spread of the mutation within species. Nevertheless, in some situations, random genetic drift can overwhelm selection and lead to the fixation of such a mutation, particularly if the reduction in fitness is modest. Indeed, it is not uncommon for partial hybrid sterility in plants to be caused by heterozygous chromosomal rearrangements that evolved in a single mutational step [4,8]. Differentiating between these alternative genetic pathways to postzygotic isolation – one versus multiple mutational steps – can help identify which evolutionary processes contribute to species divergence.

To determine whether hybrid incompatibilities evolve in multiple steps, as predicted by the Dobzhansky-Muller model, it is necessary to pinpoint the causal genetic changes at the molecular level. But even if the Dobzhansky-Muller model is confirmed, it provides no expectation as to which kinds of molecular genetic changes cause postzygotic isolation. Are there predictable genetic pathways to incompatibilities? What types of molecular interactions cause hybrid dysfunction? The Dobzhansky-Muller model is also agnostic about the evolutionary processes that cause divergence within species. Do the initial mutations increase in frequency by random genetic drift or by natural selection because they benefit the native species for some reason that is incidental to their eventual contribution to reproductive isolation? In several plant systems, the molecular variants that cause hybrid inviability and sterility have recently been identified, providing some of the first hints at answers to these fundamental evolutionary questions. Here, we focus on exclusively nuclear-encoded hybrid incompatibility genes but point the reader to several excellent reviews of cytoplasmic male sterility [9,10] and the population genetic theory for how cytonuclear incompatibilities might evolve [11,12].

Recent advances

Two-locus hybrid incompatibilities

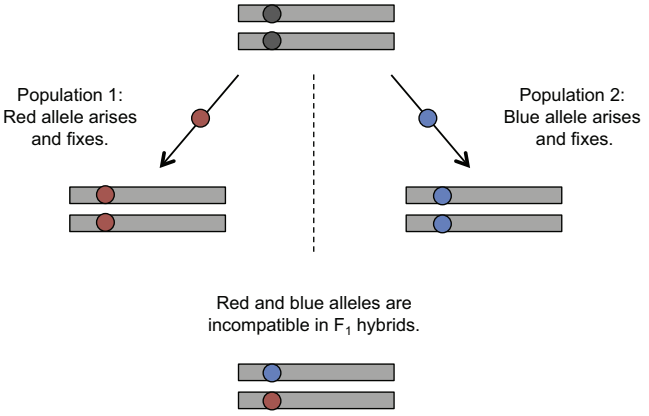
In the classic model of speciation, hybrid incompatibilities are thought to evolve as a by-product of adaptation to different environments [13]. Some of the best evidence for this idea comes from recent work on hybrid necrosis, a form of plant hybrid inviability characterized by necrotic lesions, wilting, and inhibited growth [14]. A remarkable commonality has emerged among cloned hybrid necrosis genes: all encode proteins involved in plant defense against bacterial or fungal pathogens, and incompatible allelic combinations appear to induce autoimmune-like responses [15]. The plant immune system is a tightly coordinated network of proteins that recognize pathogen invasions and elicit a suite of cellular defense responses [16,17]. One might imagine that plant-pathogen molecular coevolution, occurring in independent populations with unique pathogen communities, could lead to hybrid mismatches between interacting components of the immune system that result in hyperactivation of defense responses in hybrid offspring. Indeed, two-locus incompatibilities between pathogen resistance genes and their interacting partners have been implicated in hybrid necrosis between divergent strains of *Arabidopsis thaliana* [18-20], between the *indica* and *japonica* subspecies of Asian cultivated rice [21], and between wild and domesticated species of tomato [22] and lettuce [23]. For a few of these loci, alleles that confer necrosis differ by several amino acid changes from ancestral alleles, perhaps consistent with a sustained fine-tuning of these proteins to improve pathogen recognition.

Other recent studies suggest that two-locus hybrid incompatibilities can also readily evolve in the absence of natural selection. Based on his early genetic analyses of hybrid sterility between the *indica* and *japonica* varieties of *Oryza sativa*, Oka suggested that defects in pollen development might be caused by loss-of-function alleles at different duplicate genes in each parent [24]. Postzygotic isolation might evolve passively then, due to degenerative mutations and genetic drift acting on different paralogs (genes related by duplication within a genome) in diverging populations [25,26]. Only recently has the cloning of several plant hybrid incompatibility genes provided empirical evidence for this idea. Indeed, hybrids between different strains of *A. thaliana* arrest as early embryos when they carry loss-of-function alleles at duplicate copies of the essential histidinol-phosphate amino-transferase gene (*hpa1* and *hpa2*) [27]. Likewise, in two distinct *Oryza* crosses, null alleles at duplicate genes confer gametic male sterility [28,29]. Mizuta *et al.* [28] showed that pollen from *indica-japonica* hybrids fails to germinate when it carries loss-of-function alleles – one from each parent – at two duplicate genes of unknown function, *DOPPELGANGER1* and *2* (*DPL1* and *DPL2*). Similarly, pollen sterility in hybrids between *O. sativa japonica* and an Amazonian wild rice, *Oryza glumaepatula*, is caused by nonfunctional alleles at duplicate loci *S27* and *S28* that both encode the mitochondrial ribosomal L27 protein (*mtRPL27*) [29]. In this case, one lineage – *O. glumaepatula* – lacks the duplication; pollen is defective when it carries a loss-of-function allele at *S28* from *O. sativa* and is missing the *S27* paralog (by virtue of inheriting the corresponding genomic region from *O. glumaepatula*). An extraordinary feature of each of these systems is that loss-of-function alleles have evolved repeatedly. In *A. thaliana*, roughly three-quarters of plant collections carry one of six possible loss-of-function alleles at either *hpa1* or *hpa2* [27]. In *Oryza*, several different disruptive mutations have arisen in closely related species for both the *DPL1/DPL2* and *S27/S28* incompatibilities [28,30]. These findings, along with the rich history of whole genome duplication in plants, suggest that the divergent resolution of gene duplicates via mutation and genetic drift might be a common source of postzygotic isolation in plants.

Single-locus hybrid incompatibilities

In addition to the cases described above, studies have occasionally discovered hybrid incompatibilities that map to single genetic loci [31,32], which might be taken as prima facie evidence that postzygotic isolation can evolve via a single mutational step. Like the fixation of an underdominant chromosomal rearrangement, the establishment

Figure 1. The Dobzhansky-Muller model for a single-locus hybrid incompatibility



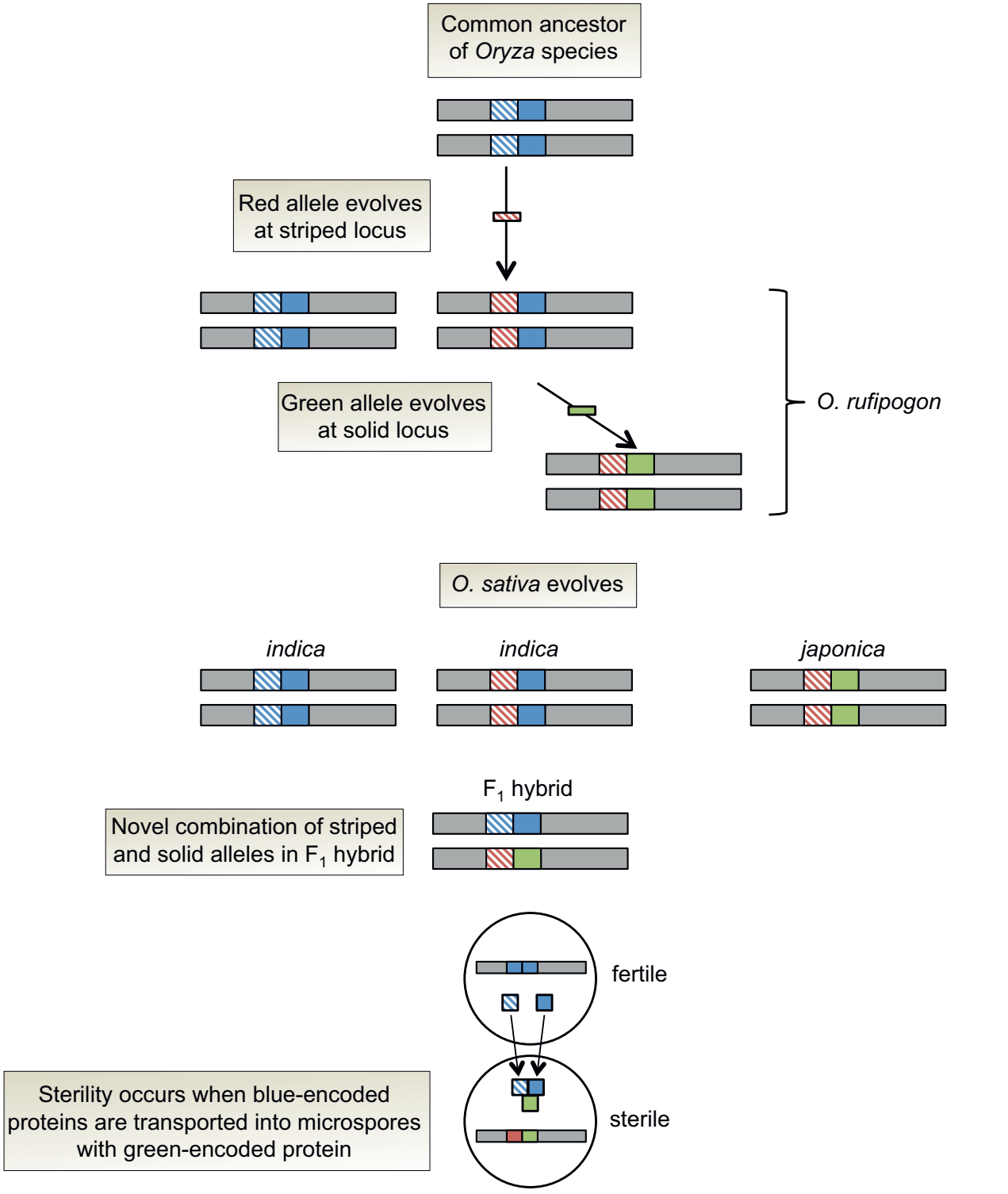
An ancestral population splits into two geographically isolated populations that diverge genetically and eventually fix different alleles (red or blue) at the same locus. In the F_1 hybrid, these two derived alleles are incompatible. Note that hybrid incompatibilities can just as easily arise between ancestral and derived alleles if two or more rounds of mutation and fixation occur within a lineage.

of a new sterility- or inviability-causing allele requires a hefty contribution from genetic drift to outweigh selection against unfit heterozygotes. But, if instead, a single-locus hybrid incompatibility is conferred by two or more alleles that evolve *independently* – implying multiple mutational steps – it is possible to circumvent any initial fitness valley within species [33] (Figure 1). The recent cloning of the single-locus hybrid incompatibility gene *OAK* [34], which encodes a receptor-like kinase (RLK) and causes reduced growth and developmental abnormalities in interpopulational hybrids of *A. thaliana*, supports just such a multiple-step scenario. Indeed, the two incompatible *OAK* alleles are 9% divergent at the amino acid level, with 55 of 152 residues differing in a key malectin-like domain [34]. With such extreme levels of sequence diversity, it is reasonable to infer that intermediate, viable genotypes predated the current incompatible pair of alleles. Although its adaptive significance is unclear, the occurrence of *OAK* within a highly variable tandem array of *RLK* genes suggests that high rates of gene conversion and illegitimate recombination may have contributed to its evolution [34].

The molecular characterization of three additional, single-locus incompatibilities between *indica* and *japonica* rice varieties also suggests the involvement of multiple mutational steps. The *S5* incompatibility locus causes embryo sac abortion in *indica-japonica* heterozygotes, but certain "wide-compatibility" varieties carry neutral alleles and can, therefore, produce fertile progeny when crossed to either subspecies. Originally described by Ikehashi and Araki as a simple, three-allele system [31], a reasonable assumption has been that the neutral allele represents an intermediate step that allowed the *indica-japonica* incompatibility to evolve without a fitness cost [35,36]. Upon closer inspection, however, genetic mapping of the *S5* locus has revealed that hybrid female sterility is regulated by three, tightly linked genes – *ORF3*, *ORF4*, and *ORF5* – and that haplotypes vary substantially among strains of *indica*, *japonica*, and wild rice [37,38,39]. During female sporogenesis, "killer" alleles at *ORF4* and *ORF5* cause endoplasmic reticulum stress that results in premature programmed cell death and embryo sac abortion, but these effects can be rescued by a "protector" allele at the adjacent *ORF3* gene. This killer-protector combination appears to be the ancestral genotype and is at high frequency in the wild species *Oryza rufipogon* and *Oryza nivara*, as well as in the outgroup species *O. glumaepatula* [39]. In contrast, the typical *indica S5* haplotype has a deletion in *ORF4* that incapacitates its killing function, and the typical *japonica* haplotype carries mutations that disable both the *ORF5* killer and *ORF3* protector. The *S5* incompatibility causes an aberrant, gain-of-function phenotype in *indica-japonica* hybrids that carry killer alleles at *ORF4* and *ORF5* but lack the protector allele at *ORF3*.

In the second case, Long *et al.* [40] fine-mapped the *Sa* locus to two distinct, tightly linked loci: *SaM* encodes a small ubiquitin-like modifier (SUMO) E3 ligase-like protein, and *SaF* encodes an F-box protein. Hybrid plants that are heterozygous at *SaM* and also carry *indica* alleles at *SaF* are semi-sterile because haploid pollen that inherits the *japonica SaM* allele fails to develop properly. To explain the surprising result that epistasis among *three* alleles is required for abortion of *japonica SaM*-carrying microspores, the authors propose a complicated model in which *indica*-encoded SaM and SaF proteins are transported between haploid microspores during early pollen development to kill gametes that inherit the *japonica SaM* allele [40]. The idea is that the *japonica* SaM protein is unable to move between microspores, so pollen grains that carry *indica* alleles at *SaM* and *SaF* – but do not receive the interacting *japonica* SaM protein – remain viable. For this incompatibility system to have evolved unopposed by natural selection, the *japonica SaM* allele must have spread after a "permissive" allele at *SaF* had fixed initially (Figure 2). Indeed, the current geographic distribution of *SaM*/*F* haplotypes in *O. sativa* and its wild ancestor, *O. rufipogon*, is consistent with this scenario [40]. Moreover, patterns of *SaM*/*F* haplotype variation – particularly, the finding that *japonica*-like haplotypes segregate in *O. rufipogon* but not *indica* populations – support the hypothesis of independent origins of domestication for *indica* and *japonica* [41,42]. An important, unanswered question is what caused the *japonica* haplotype to become fixed.

Figure 2. Model for the evolution of *Sa* hybrid sterility in rice



A classic, single-locus incompatibility between *Oryza sativa indica* and *Oryza sativa japonica* is conferred by two adjacent genes (depicted here as striped and solid). Semi-sterility occurs in F_1 hybrids that carry blue alleles at the striped and solid genes (*indica* haplotype) in combination with a green allele at the solid gene (*japonica* haplotype). The wild progenitor *Oryza rufipogon* carries all three haplotypes: ancestral (blue, blue), "permissive" (red, blue), and *japonica*-like (red, green). Figure adapted from [40].

In the third case, Zhao *et al*. [43] mapped the *S24* pollen sterility locus to an ankyrin-3 (*ANK-3*) gene, which Kubo *et al*. [44] later showed is dependent on an additional, unlinked locus, *Epistatic Factor for S24* (*EFS*). Like *S5* and *Sa*, the *S24-EFS* hybrid incompatibility is a gain-of-function: pollen grains with *japonica S24* alleles are aborted in *S24*-heterozygotes, but only when the plant is *also* homozygous for *japonica* alleles at *EFS*. As with *Sa*, it is possible that the otherwise deleterious *japonica S24* allele was only able to spread in a permissive, *indica*-like *EFS* background, but the necessary phylogeographic analyses have not yet been done. It is also worth noting that for both *Sa* and *S24*, certain wide compatibility varieties carry neutral alleles that rescue pollen sterility [43,45], indicating that the evolutionary histories of these incompatibilities might include alternate mutational routes.

Conclusions and future challenges

In just the last few years, plant geneticists have made tremendous progress in identifying the molecular genetic basis of postzygotic reproductive isolation. With more than a dozen genes now cloned, it is clear that plant hybrid incompatibilities usually evolve via two or more mutational steps, as is predicted by the Dobzhansky-Muller model. This conclusion flows rather easily from those cases in which hybrid dysfunction is caused by epistasis between two or more unlinked genes, but it has been less obvious for a number of classic, single-locus incompatibilities [31]. Because of several recent detailed genetic studies, however, we now know that even these single-locus incompatibilities arose by mutations in two tightly linked genes, or, at the very least, two or more amino acid changes encoded within the same gene. Thus, it is possible that most of these incompatibility alleles appeared without any reductions in fitness within species.

Of course, the key question for speciation is which evolutionary forces allow incompatibility alleles to increase in frequency and eventually become fixed within species. For a few of the cases discussed above there is evidence that natural selection (e.g. hybrid necrosis) or random genetic drift (e.g. divergent resolution of duplicate genes) may have played a role. It also appears that there are some common genetic routes to plant hybrid dysfunction. Indeed, immune system genes seem to contribute disproportionately to hybrid necrosis. As we have seen, it is even possible for the very same gene to be involved in multiple cases of hybrid dysfunction: divergent duplicate loci carry a striking number of independently derived, loss-of-function mutations. Yet, there are many hybrid incompatibilities that do not involve disease resistance or duplicate genes, and, for these systems, we are only beginning to understand the evolutionary causes of divergence. Remarkably, at least 50 loci contribute to hybrid sterility between the closely related subspecies *Oryza sativa indica* and *Oryza sativa japonica* [46]. So does this large number reflect a special propensity in rice species for evolving hybrid sterility? Given that *Oryza* flowers have six anthers with many pollen grains per ovule, a gametic pollen killer that lowers fertility by 50% might entail little or no reduction in heterozygote seed fertility. Although our current sample of plant hybrid incompatibility genes comes from only two genera (*Oryza* and *Arabidopsis*), there are a number of classic [46,47] and more recently identified [48-51] incompatibility systems that are not yet molecularly defined. As advances in genomics and DNA sequencing technologies enable rigorous genetic analysis of reproductive isolation in a number of emerging model systems, we should gain new insight into which factors affect the number and nature of hybrid incompatibilities that accumulate between plant species.

Abbreviations

ANK-3, ankyrin-3; *DPL*, *DOPPELGANGER*; *EFS*, *Epistatic Factor for S24*; mtRPL27, mitochondrial ribosomal L27 protein; RLK, receptor-like kinase; SUMO, small ubiquitin-like modifier.

Competing interests

The authors declare that they have no competing interests.

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