Trends in Genetics

CellPress

Review

Gene Regulation and Speciation

Katya L. Mack[1] and Michael W. Nachman[1,*]

Understanding the genetic architecture of speciation is a major goal in evolutionary biology. Hybrid dysfunction is thought to arise most commonly through negative interactions between alleles at two or more loci. Divergence between interacting regulatory elements that affect gene expression (i.e., regulatory divergence) may be a common route for these negative interactions to arise. We review here how regulatory divergence between species can result in hybrid dysfunction, including recent theoretical support for this model. We then discuss the empirical evidence for regulatory divergence between species and evaluate evidence for misregulation as a source of hybrid dysfunction. Finally, we review unresolved questions in gene regulation as it pertains to speciation and point to areas that could benefit from future research.

A Role for Gene Regulation in Hybrid Sterility and Inviability

Understanding the genetic basis of speciation is a longstanding problem in evolutionary biology. The major model for the evolution of intrinsic post-zygotic isolation postulates that hybrid sterility or inviability arises from negative interactions between alleles at different loci when joined together in hybrids. The regulation of gene expression is inherently based on interactions between loci, raising the possibility that disruption of gene regulation in hybrids is a common mechanism for post-zygotic isolation. Although there is accumulating evidence that changes in gene regulation play a prominent role in adaptation (e.g., [1,2]), the role of regulatory evolution in speciation has received less attention. We evaluate here the role of regulatory evolution in speciation, and we suggest, both from recent theoretical and empirical studies, that changes in gene regulation play a major role in intrinsic post-zygotic isolation. While our focus is on post-zygotic isolation, regulatory divergence may also play an important role in establishing other reproductive barriers as a byproduct of adaptive divergence (i.e., ecological speciation).

Conceptual Framework

Single-locus models of hybrid dysfunction all suffer from the problem that mutations that lower the fitness of heterozygotes (and thus cause reproductive isolation) are unlikely to become established in a new population (e.g., [3–5]). This problem was recognized by Bateson [6], Dobzhansky [7], and Muller [8,9], who suggested instead that hybrid dysfunction could arise from negative interactions between alleles at two or more loci. In the Bateson–Dobzhansky–Muller (BDM) model, alleles that are adaptive or neutral in their own genetic background are incompatible with alleles at one or more loci on the alternative genetic background (Figure 1). Thus, diverging lineages can accumulate substitutions without any loss of fitness. There is now strong empirical support for this model of intrinsic post-zygotic isolation [10].

Gene regulation is the process by which cells control the specific amount of gene product (i.e., RNA or protein) produced. Gene regulation is a complex process involving the interaction of DNA sequences, RNA molecules, and proteins, as well as epigenetic modifications. Because the interaction of regulatory elements is required for organismal function, interacting regulatory elements are assumed to be co-adapted (e.g., [11]). When co-adapted interactions between

Trends

Simulation studies suggest that hybrid incompatibilities can evolve rapidly when selection acts on regulatory pathways.

Genomic approaches have identified widespread regulatory divergence between species in *cis* and *trans*.

Cis–trans regulatory divergence increases with phylogenetic distance and has been associated with misexpression in interspecific hybrids.

Many known hybrid incompatibility genes have either a putative regulatory function or are misexpressed in hybrids.

[1]Department of Integrative Biology and Museum of Vertebrate Zoology, University of California, Berkeley, CA 94720, USA

*Correspondence: mnachman@berkeley.edu (M.W. Nachman).

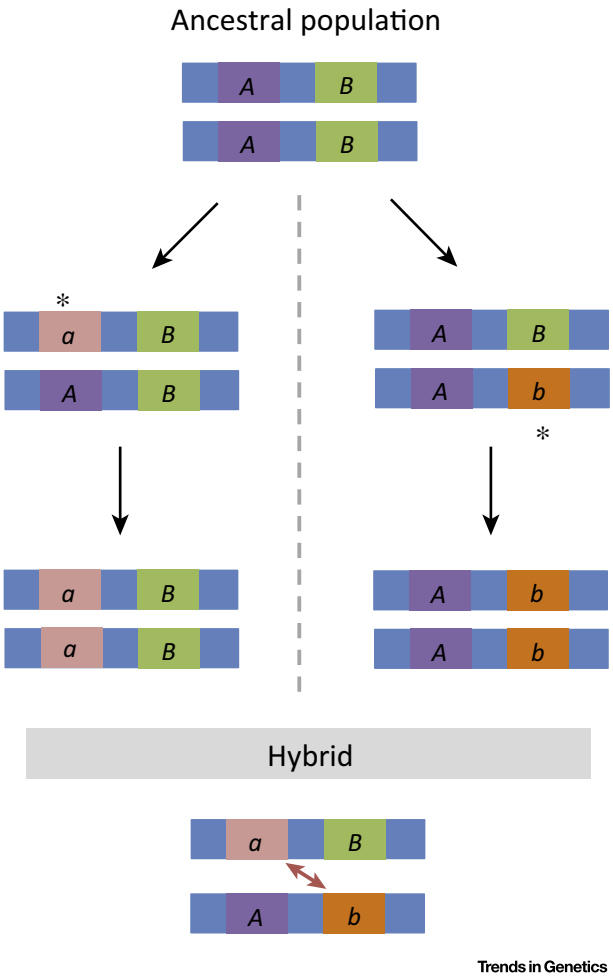

Figure 1. The Bateson–Dobzhansky–Muller Model of Hybrid Incompatibility. In the ancestral population, the genotype is *AABB*. After the two populations are isolated, new mutations arise independently on each lineage as indicated by the asterisks. In one population, *A* evolves into *a*, in the other population *B* evolves into *b*. In hybrids, negative interactions between the *a* and *b* alleles can result in sterility or inviability. The *a* and *b* alleles are found together for the first time in hybrids, explaining how this incompatibility could evolve without either lineage experiencing an intermediate state of reduced fitness.

regulatory elements are disrupted, downstream targets of these elements may be misregulated. While disrupted interactions between any of pair of regulatory elements or sequences could result in hybrid incompatibilities, the process of transcription initiation has received the most attention. While we focus mainly on transcriptional control, divergence between regulatory elements affecting other levels of gene regulation (e.g., translation) may also play a role in speciation.

Transcription is regulated by the interaction of *cis*-regulatory elements and *trans*-acting factors. *Cis*-regulatory elements are stretches of non-coding DNA (e.g., promoters, enhancers) that act as binding sites for *trans*-acting factors to regulate mRNA abundance. In the simplest case, the *trans*-acting factors are transcription factor proteins, although other proteins have also been known to act in *trans* to regulate gene expression [12]. Mutations in *cis*-regulatory regions or in transcription factors can affect mRNA abundance. Transcription factors frequently interact with multiple downstream target sequences and thus may be pleiotropic. By contrast, a single gene may have multiple *cis*-regulatory regions that regulate it