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Molecular Biological Mechanisms of Speciation

Michael R. Rose and W. Ford Doolittle

Summary. Growing recognition that much of the evolutionary history of eukaryotic genomes reflects the operation of turnover processes involving repetitive DNA sequences has led to the recent formulation of models describing speciation as a consequence of such turnover. These models are of three general kinds: those attributing hybrid infertility to the process of transposition, those attributing hybrid infertility to mispairing between chromosomes of divergent repetitive DNA composition, and those assuming that change in repetitive DNA's can reset coordinated gene regulation. These models are discussed with respect to the kinds of evidence needed for their corroboration and to their significance for questions related to macroevolutionary punctuated equilibria and genetic revolutions.

Recent discoveries in molecular biology have prompted speculation regarding their significance for evolution, with new synthetic hypotheses receiving great attention (*1–16*). Unfortunately, the intuitive appeal or conceptual breadth of a theory is not an infallible guide to its validity. Here we examine the empirical status of some of these new hypotheses in evolutionary molecular biology, those relating the origin of species to the evolutionary behaviors of repetitive DNA's.

Because of the diversity of new molecular biological proposals for speciation mechanisms, we find it convenient to group them under three headings, and to assess each of them in terms of four lines of evidence. At least these four are needed to test the new molecular biological proposals properly. First, there must be a known biological effect that can lead to reproductive incompatibility. Second, the molecular mechanisms presumed responsible for that effect must be known to operate in species in which the effect is observed. Third, there must be evidence that molecular mechanism and biological effect are coupled. Fourth, there must be parallels between biological effect and speciation, such as instances within related species in which the effect can reasonably be interpreted as primarily responsible for, and not secondarily a consequence of, reproductive isolation.

By speciation, we mean the establishment of biological characteristics (i) that preclude fertilization of members of one population by those of another (prezygotic reproductive isolation) or (ii) that give rise to pathologies among hybrids, or hybrid descendants, which in turn preclude gene flow between these populations (postzygotic reproductive isolation) (*17*).

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Molecular Mechanism I: Genomic Disease

The view that many, although not all, transposable elements provide no functional benefit to the organism is now commonplace (*11–14*). Whether or not such elements decrease organismal fitness is as yet uncertain. It is clear on theoretical grounds that transposable elements can decrease fitness and yet be maintained within Mendelian populations (*18*).

Transposable elements are potentially important for the phyletic (within-species) evolution of both Mendelian and asexual populations (*10, 14, 19*). An analogy with disease suggests that they might also be important in the formation of new species, a process that can be uncoupled from phyletic evolution. If an isolated population has either lost or failed to acquire transposable elements that have spread throughout remaining populations of the species, then it may lack some property establishing immunity to these elements. Matings between individuals of that isolate and individuals of other populations could lead to abnormalities resulting from proliferation of the novel, disruptive, transposable element (*20*). Such abnormalities could lead to sterility of F_1 or F_2 hybrid progeny, thereby establishing postzygotic reproductive isolation. To avoid gamete wastage, natural selection might then act to establish behavioral or mechanical (or both) prezygotic barriers to mating. This is in effect a "genomic disease" model for speciation.

At present, *Drosophila melanogaster* is the only studied organism providing full corroborative evidence for the potential action of genomic disease in speciation. This evidence has already prompted a number of suggestions concerning evolutionary mechanisms, from which we derive our generalized mechanism (*8, 11, 13*).

The first line of evidence, that for biological effect, comes from the phenomenon of hybrid dysgenesis. Hybrid dysgenesis arises in one of the two reciprocal male-female crosses, usually males from recently wild-caught strains crossed with females from long-established laboratory strains (*21, 22*). It is characterized by various associated germ line dysfunctions including high mutability, frequent chromosomal rearrangements, male recombination (normally absent in *Drosophila*), failure of early embryonic development, and sterility due to germ line extinction in both males and females. This is just the sort of syndrome one expects from genomic disease. The only puzzle is the ostensible normality of the somatic tissue. However, this may be because of some "committed" property of somatic cells, reflecting the "disposability of the soma" (*23*), for the host or the transposable element.

The second test, that for an appropriate molecular mechanism operating in *D. melanogaster*, is also met. The *D. melanogaster* genome has many families of transposable elements. In fact, much of the dispersed middle-repetitive DNA of this organism is "copia-like" in nature. Such elements vary in chromosomal location, increase rapidly in number in cultured cells, show typical transposon-like element structure and generate flanking repeats of target site sequences upon insertion, and they have been unequivocally associated with certain well-characterized spontaneous mutations (*8, 9, 24*).

The third test, that for coupling of molecular mechanism (transposition) and biological effect (hybrid dysgenesis), is also met. There are two distinct forms of hybrid dysgenesis, arising from the P-M and I-R interaction systems (*22, 25*). These interaction systems appear to involve characteristic transposable elements (P factors and I factors, respectively). The P-M interaction system seems to involve transposable element activation upon fertilization by sperm from factor-bearing (P) strains of eggs from factor-free (M) strains, and may reflect the absence of repressor-like determinants in the latter (*22, 26*). Evidence for this interpretation of hybrid dysgenesis was at first confined to patterns of transmission, especially chromosome contamination (*26*), but detailed cytological work has since been completed (*27*) and molecular biological evidence has now been published for the P-M system (*11, 12*). Some aspects of the biology, of course, remain to be resolved (*28*). Outstanding problems concern the cellular properties underlying immunity of P and I strains to P and I factors, and the evolution of such factors in natural populations. It also remains an open question whether these factors have been lost by those laboratory strains susceptible to hybrid dysgenesis or have been recently acquired by wild populations (*25, 29*). In either case, both processes could act in nature to establish biological barriers to gene exchange between populations that have been physically isolated for some time, provided only that these factors have not been lost by laboratory strains because of some special feature of laboratory conditions.

The fourth test, that for real parallels between hybrid dysgenesis and the biology of interspecific sterility in *Drosophila*, may also be met. At the level of gonadal anatomy, parallels between P-M hybrid dysgenesis and *D. melanogaster* and *D. simulans* hybrid pathologies are striking (*30*). Parallels between the biology of I-R system dysgenesis and that exhibited by crosses between sibling species of the *D. pseudoobscura* group have also been drawn (*31*).

Although no form of hybrid dysgenesis in *D. melanogaster* at present precludes gene flow between any known pair of populations, the development of several such dysgenesis systems could give rise to reciprocal pathologies such that F_1 hybrids of either sex cannot backcross to either population, as pointed out by Bingham, Kidwell, and Rubin (*12*). In any case, the genomic disease model meets all four of our proposed tests in *Drosophila*. Whether this is because of biological features peculiar to the genus, or because of the intensive scrutiny it has received in general, remains unclear.

Molecular Mechanism II: Mechanical Genome Incompatability

This potential mode of molecular biological speciation, like genomic disease, could depend on the activities of transposable elements, as well as on such processes as unequal crossing-over and gene conversion, which also alter the positions, numbers, or sequences of clustered and dispersed repetitive DNA's (*32*). Like genomic disease, this mode does not require that these DNA's be functional. It does require that alterations affecting them disrupt chromosomal interaction processes in such a way that hybrids formed between previously interbreeding populations are effectively sterile.

Most simply, disruptions in recognition could lead to meiotic nondisjunction: that is, the failure of chromosomes to pair and separate properly during the formation of gametes (*3–5, 10, 15*). Flavell suggests, for instance, that "many of the genomic differences between certain cereal species are due to rapid sequence turnover. If some of these differences were contributors to loss of pairing and recombination in hybrids between individuals before speciation, then sequence turnover could have been a major contributor to speciation" (*5*).

The biological effect referred to here is reduction in meiotic chromosome recognition, not the gross chromosomal imbalance produced by mechanisms like translocation (*33*). Corroborative evidence for this biological effect has been taken from many observations showing that viable hybrids between already-established species without gross karyotypic differences are often nevertheless infertile. This infertility is often correlated negatively with meiotic chromosome pairing and chiasmata formation, and positively with interspecific divergences in the sequences and relative amounts of noncoding clustered and dispersed repetitive DNA's (*4, 5, 34–37*). Such correlations are most firmly established for cereals, but even here genetic variables other than differences in chromosomal architecture play significant roles in suppressing or enhancing homeologous chromosome pairing during meiosis (*4, 5*). From cytogenetic analyses of interspecific *Lolium* and *Festuca* hybrids, Rees and co-workers conclude that "what is perhaps most deserving of emphasis overall is the completeness of the synaptonemal complexes, the effectiveness of pairing . . . despite, in each case, a massive disparity in length and DNA content between homeologous chromosomes" (*35*). In *Drosophila*, substantial quantitative alterations in heterochromatic repetitive DNA's affect recombination but not gametogenesis, and even extensive multiple inversions seem insufficient to effect reproductive isolation in the *repleta* subgroup of this genus (*15, 34, 38*). Hawley, following an earlier suggestion of Sandler, has concluded that meiotic chromosome pairing in *D. melanogaster* may be determined by a quite limited number of chromosomal sites, four in the case of the X chromo-

some (*39*). As Flavell notes in a more general context, "whether all sequences of a chromosome contribute to the homology necessary for recombination or whether only a subset is involved is unknown" (*5*). Thus the suggestion that genomic events that can indeed promote quantitative and qualitative divergence between the repetitive DNA's of homologous chromosomes in physically isolated populations can also have the accidental biological effect of postzygotic reproductive isolation remains an intuitively appealing hypothesis that has yet to pass the first test in any biological group and has failed it in at least one, *Drosophila*.

Turnover of repetitive sequences can, at least potentially, have biological effects on chromosome interactions of quite a different sort. Such interactions involve nonhomologous chromosomes of a haploid set and result in predictable spatial associations between them in nonmeiotic nuclei, as shown by Bennett and others for plant cells (*40, 41*) and by Manuelidis *et al.* for animal cells (*42*). In cereals, chromosomes of haploid sets most frequently are of such configurations that the most similarly sized pairs of long arms and the most similarly sized pairs of short arms are in proximity. If three-dimensional interchromosomal interactions have significant effects, then relative arm lengths will be preserved within interbreeding populations in spite of the amplification or loss of repetitive DNA's (*40–42*). [For instance, in the genus *Plethodon*, relative lengths and arm ratios of corresponding chromosomes remain constant despite fourfold interspecific variation in total chromosome length that can be attributed to the differential expansion of different families of repetitive DNA's (*37*)]. The appropriate parental haploid set configurations could also be retained in F_1 hybrids between populations that have divergent DNA content (*40–42*). But they would not be retained in most F_2 progeny. The resulting disruption of the (as yet unknown) function (or functions) of nonhomologous chromosome associations should thus reduce the fitness of hybrid populations. The potential speciation promoting biological effect is obvious. What is needed is more evidence.

On the other hand, there is ample evidence for mechanism. Almost all eukaryotic genomes have both clustered and dispersed repetitive elements, and frequent rearrangements affecting these elements result in their rapid "turnover" (*14, 32, 34*). Processes that bring about such turnover are well described (*1*), and at least three of them—transposition, unequal crossing-over, and gene conversion—can explain the "concerted" evolutionary behavior of such repeats, behavior that leads to the general observation of greater within-species than between-species sequence homogeneity in related families of repeats. These processes effect homogenization in different ways and with different consequences for chromosome structure. However, Dover addresses them within a single conceptual framework termed "molecular drive" (*1*). He makes the novel prediction that, if rates of repeat sequence family homogenization within genomes are slow compared to rates at which sites occupied by repetitive elements are randomized between genomes in a sexually reproducing population, then new variant sequences can be fixed within large families regardless of the effect of fixation on phenotype. This will be true if variance between individuals, in terms of their content of "new" and "old" sequence variants, is too small to affect relative fitness. Only rigorous theoretical analyses can define the severity of the constraints under which this process can provide a "cohesive mode of species evolution," and such speciation models do not differ from others in the need to meet tests for coupling and biological effect.

Nevertheless, given the ability of all such processes to maintain some degree of repeat sequence homogeneity within populations while promoting repeat sequence divergence between populations, there should be no difficulty in coupling mechanism and effect. The difficulty is, as noted above, in establishing effect, and this difficulty is twofold. We need stronger evidence that disruptions of the association between homologous chromosomes during meiosis or between nonhomologous chromosomes in somatic cells which are sufficient to cause hybrid sterility are the direct result of quantitative or qualitative changes in repetitive sequences. We also need evidence that such changes are the primary cause, rather than the secondary and inevitable consequence, of reproductive isolation. It will be difficult to obtain either with the use of data from already isolated populations showing reduced hybrid fitness, since this can have many causes. It may be possible to obtain both with carefully constructed laboratory stocks derived from a single species. Unfortunately, such work is currently limited to *Drosophila* (*11, 12, 21, 22, 24–31*). As Flavell *et al.* point out, "the genomes of organisms with large DNA contents may diverge more rapidly between populations than the genomes of organisms with low DNA contents" . . . and thus "any role that 'macromutation' or nonadaptative changes play in speciation may be different in organisms such as *Drosophila*, primates, and wheat . . ." (*5*).

Molecular Mechanism III: Genome Resetting

This potential mode of molecular biological speciation also depends upon noncoding repetitive DNA's; but, unlike either genomic disease or mechanical genome incompatability models, it requires that at least some such DNA's be functional and that this function depend upon sequence. In particular, they must be regulatory elements whose positions and sequences influence developmental pathways in complex and coordinated fashions (*3, 6, 7*). Coordinated changes in position and sequence could then alter such pathways in potentially beneficial ways, leading to rapid divergences between temporarily isolated populations (*3, 6, 7, 10*). Even were such alterations selectively neutral, they could lead to prezygotic reproductive isolation through coincidental divergence of mating behavior or coincidental postzygotic incompatability in germ line or somatic cell development or function in hybrids. Speciation models of this sort are, as pointed out by Dover, Gould, Macgregor, Smith, Stanley, Schopf, and very many others (*3, 15, 37, 43–48*), "Goldschmidtian" in that they assume that major evolutionary change requires something more than the gradual accumulation of single mutations affecting single genes, and in that these changes accompany the development of reproductive isolation.

Most such models find their deepest molecular biological roots in a scheme for eukaryotic gene regulation first articulated about a dozen years ago by Britten and Davidson [see (*7*)] when short repeats seemed likely a priori to be operator-like regulatory modules, with those of one family being associated with a "battery" of coordinately regulated structural genes. An attractive feature of this scheme was the facility with which it might account for the coordinated reprogramming of complex developmental pathways during speciation, through the simple expedient of "saltatory" replacement of one family of dispersed operator-like or regulator-like repeat sequences by another.

In 1979, Davidson and Britten reformulated their model (*7*). Regulation was to be effected through RNA:RNA molec-

ular hybrids formed between small regulatory RNA's, again the products of one or more coordinately controlled batteries of repeat sequence families, and the transcripts of other repetitive families known to be embedded within nascent primary transcripts. The model remains modular in its original sense, "the control logic we [Davidson and Britten] originally postulated is retained," and the evolutionary corollaries come through intact.

A similar control logic underlies many of the evolutionary speculations of those who might not otherwise accept the kind of unitary hypothesis for regulation of gene expression upon which these corollaries so clearly depend (*3, 6, 10, 43–46, 49*). Gillespie *et al.* (*6*), for instance, present an evolutionary model in which "genome resetting . . . is mediated by newly amplified DNA. Though genome resetting may have a role in genetic programming, e.g., during development, the evolutionary consequence of successful genome reorganization is speciation. . . . It is argued that these reorganizations serve to establish new genetic programs in development and differentiation, which define the morphological and physiological characteristics of new species."

Reprogramming of development can, of course, lead directly to prezygotic or postzygotic reproductive isolation. Such reprogrammings, especially as manifested morphologically, are often used provisionally to define as species isolated (or extinct) populations whose mating it is impracticable (or impossible) to force. Thus both the required isolating biological effects and real parallels in speciating populations are well known. It is also clear that there are quite general mechanisms which might bring about the required changes in repeat sequence families. These could be the same well-described turnover mechanisms that might lead to mechanical genome incompatibility.

The difficulty comes in establishing coupling between such genome turnover mechanisms and developmental reprogramming. Falsifiably explicit formulations of genome resetting models make specific demands on genome structure and the ways in which it can be altered without serious detrimental effects. Dispersed repetitive sequences of specific families must occupy reasonably well-defined positions with respect to coordinately regulated genes, and it must be possible to replace them with other, differently regulated, repeats in an orderly fashion.

We know of no specific instances in which both of these demands are met, nor of any coherent body of evidence that either is generally met in eukaryotic genomes. Data quite recently obtained by Zuker and Lodish (*50*) with *Dictyostelium* do show the regulated co-transcription of members of one repetitive DNA sequence family with some coordinately regulated messenger RNA's, but comprise, as these authors note, "the first case in which specific repetitive sequences are linked to a set of developmentally regulated genes." There are many other examples from many other systems that provide no support for such a unitary model for the regulation of eukaryotic gene expression (*51, 52*), and Davidson and Posakony have recently remarked that "despite their ubiquity, their quantitative prominence, their apparent developmental regulation and the amount of interest they have aroused, the [dispersed] repetitive sequence transcripts of animal cells remain a phenomenon in search of a physiological meaning" (*53*).

This does not mean that coordinately regulated genes may not share short common regulatory sequences; in some cases they clearly do (*51, 54*). It does mean that these sequences may not in general be so large (> 100 base pairs) or so frequent in the genome (> ten copies) as to be recognizable as dispersed repetitive sequences in the usual kinds of DNA renaturation analyses (*7*). It therefore also means that what we do know about those genomic turnover processes which govern the evolution of identifiable repetitive DNA's may have no revelance whatever to the evolutionary behavior of regulatory sequences. Perhaps in recognition of these difficulties, several formulations of genome resetting models (*6, 10, 16, 43–46, 49*) do not refer explicitly to the schemes of Britten and Davidson (*7*). Instead, they only allude to the potential regulatory consequences of concerted genome turnover in repeat sequence families and to the more general notion that higher order genome structure governs genome function (*15*).

In discussing the concerted evolutionary behavior of repetitive sequences, Dover (*1*) suggests that, in some instances "interpopulation discontinuities" might reflect divergence of members of tandemly arrayed multigene families, whose homogeneity within populations is maintained by unequal crossing-over or gene conversion (or both). This suggestion is not subject to the same objections as those involving the coordinated reprogramming of dispersed and functionally differentiated genes, and differs from more traditional models of speciation in the nature and possible rapidity of the mechanism by which variant alleles establishing reproductive isolation are fixed within physically isolated populations. However, the evolutionary histories of the coding regions of most known tandemly arrayed multigene families (*55*) are histories of either (i) strong interspecific conservation (ribosomal RNA genes, histone genes), (ii) intraspecific homogenization coupled with rates of interspecific divergence not substantially higher than those expected for single-copy genes (certain globin gene pairs), or (iii) functional and structural divergence between coding regions that have remained clustered but evaded homogenization, or that have given rise to dispersed members of differentiated function (insect chorion genes, vertebrate globin genes in general, and actin and tubulin genes). Noncoding regions of tandem arrays, in particular the putative nontranscribed promoter regions of ribosomal DNA arrays, do show intraspecific structural and, in the case of *Drosophila*, functional divergence (*56*). The extent to which this divergence is actually accelerated by "molecular drive," and thus has a speciation-promoting potential beyond that of selection or drift operating on coding or noncoding regions of single-copy genes, remains to be established.

Relevance to the Evolutionary Biology of Speciation

In the past, speciation has been dealt with almost entirely within evolutionary biology. Accordingly, we now address the relevance of molecular biological mechanisms of speciation to some of the major issues in that field.

1) It should be pointed out that there are cases where none of the proposed molecular mechanisms need be involved, and that few proponents of molecular biological mechanisms claim complete generality. For example, circumstantial evidence suggests that speciation can occur in insects as a result of food preference differentiation dependent on a few loci affecting habitat selection and resource utilization (*57*). In frugivorous dipterans (such as *Rhagoletis*), reproductive isolation may arise from the use of different monotypic hosts as both food sources and mating territories, and there are cases of single loci controlling such habitat selection in these species. Interspecies hybrid infertility can indeed be absent, corroborating the assumption of behavioral premating isolation (*57, 58*).

2) Another issue in evolutionary biol-

ogy concerns the relative importance of prezygotic and postzygotic isolating mechanisms in initiating speciation (*17, 59*). Evidently, the genomic disease and mechanical genome incompatibility mechanisms act postzygotically only. But this is not true of genome resetting, which could conceivably act so that postzygotically compatible individuals from different populations become mechanically or behaviorally incompatible as mates. At present, there is no evidence that the genome resetting mechanism has been involved in any such speciation event.

3) The evolutionary controversy attracting greatest attention is that surrounding the "punctuated equilibrium" interpretation of evolution, espoused by Eldredge, Gould, and Stanley (*43–45, 47*). This view is that most evolutionary change occurs at the time of speciation, with stasis between speciation events. It has been suggested that evidence concerning genome evolution and molecular mechanisms of speciation provides support for this theory (*3, 6, 44, 46*). Indeed, genome resetting hypotheses clearly derive much of their current appeal from their apparent consonance with this view of the fossil record. The necessity of this association has been explicitly rejected by Gould: "there is little relationship or, rather, little constraint imposed by the existence of punctuated equilibrium upon modes of speciation" (*47*).

4) Another speciation controversy centers on the relative importance of natural selection in the divergence of populations creating species versus fortuitous differentiation of population gene pools leading to reproductive isolation. Darwin seemed to view speciation as a by-product of natural selection acting in different ways on isolated breeding populations (*60*), and this view has retained adherents (*61*). However, there are those who regard speciation as resulting from fortuitous genetic differentiation, such as that brought about by the fixation of different chromosomal configurations through sampling effects in small populations (*33*). Of the three molecular mechanisms of speciation discussed, two are essentially fortuitous: genomic disease and mechanical genome incompatibility. The third, genome resetting, can involve natural selection. Thus, the relative merits of these mechanisms reflect on the relative merits of "adaptive" and "accidental" theories of speciation.

5) A fifth issue concerning speciation is directly dependent on the validity of the proposed molecular mechanisms of speciation. Before the widespread utilization of analysis of enzyme variants in surveys of genetic variability within and between species, it was supposed by some that speciation entailed a "genetic revolution" involving changes in allelic composition at most loci (*61*). But in fact there may be a substantial fraction of functional protein-coding loci which is not affected by speciation (*62*). Thus it has been proposed that a distinct class of genes is involved in speciation, the remainder of the genome neither contributing to the process nor being affected by it (*63*). If we broaden the definition of "gene," then all three of the mechanisms of speciation discussed here fit with this new view and suggest ways in which it could be elaborated.

Overall then, these new theories of speciation are of significance for some, but not all, of the ongoing speciation controversies in evolutionary biology. It certainly is not the case that these novel speciation mechanisms require the overthrow of neo-Darwinism, interpreted broadly. Indeed, speciation mechanisms of this kind have been called for by population geneticists who would certainly regard themselves as neo-Darwinians.

Conclusion

One of the appealing aspects of these molecular biological models is that they unite two hitherto separate fields. Nevertheless, the appraisal of new hypotheses must be by means of experiment, rather than by comparisons based on overall scope and intuitive plausibility. The implausible or unlikely may in fact be true, as hybrid dysgenesis illustrates. Without this now reasonably well understood phenomenon, the genomic disease mechanism of speciation would seem farfetched indeed. Conversely, the heuristic powers of genome incompatibility and genome resetting mechanisms obscure the present lack of ultimately convincing experimental support.

Each of the adduced mechanisms requires further investigation. For genomic disease, there is a need for some assessment of its generality; perhaps it only acts in *Drosophila*. For mechanical genome incompatibility, evidence concerning the postulated biological effects is wanting. Some evidence for intraspecific geographical divergence in repetitive sequences affecting chromosomal disjunction, above and beyond effects on recombination, would be helpful. Further elucidation of nonhomologous chromosome-chromosome interactions, and their dependence on chromosome structure, is also essential. Finally, for genome resetting we need to gain at least some knowledge of the functional significance of chromosome structure and the role of repetitive DNA's in determining such function.

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