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INSIGHTS FROM MODEL SYSTEMS
Mice and the Role of Unequal Recombination in Gene-Family Evolution

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Introduction

As in classical views of organismal evolution, molecular evolution is often portrayed as a painfully slow process of mutation and natural selection, in which "blank slates" of DNA sequence ultimately evolve into genes, one nucleotide at a time. We have come to learn that the evolution of species over time is not uniform but occurs in fits and starts. It is probably not coincidental that genomes evolve likewise.

A primary driving force in genome evolution is duplication. Very efficiently, duplication enables the recruitment of preexisting genetic material as a substrate for the formation of novel functional units, thereby catalyzing rapid and saltatory genetic changes. Extra gene copies created through duplication may ultimately diverge to perform related but adapted functions. The mammalian globin family, which has evolved a highly coordinated process of tissue- and stage-specific expression of developmentally specialized genes from a single ancestral gene, exemplifies this process (Hardison 1998; also see Goodman 1999[in this issue]). The mammalian genome contains numerous gene families, some with as many as several hundred members, called "superfamilies." The immunoglobulin superfamily is an extreme example (Hunkapiller and Hood 1989).

Although duplication takes many forms, sometimes involving a whole chromosome or genome, a more common event is local duplication of one or a few genes by unequal recombination. This can occur by pairing of homologous but nonallelic sequences (fig. 1). Initial duplications of single-copy genes can be catalyzed by repetitive elements, such as Alu or L1 (Cross and Renkawitz 1990), and subsequent events can occur within the duplicated genes themselves, creating new, hybrid genes. Depending on the number of genes in the family and the location of the crossover events, single unequal recombination events can dramatically increase the gene-copy number of a family.

Recombination Giveth, and Recombination Taketh Away

Immediately following duplication via unequal recombination, a new gene or DNA fragment would be identical to the preexisting genetic information. In molecular evolution's success stories, new copies of a gene diverge, ultimately acquiring a novel, beneficial function for the organism. However, duplicated sequences are susceptible not only to reversion of the original duplication but also to gene conversion, the nonreciprocal transfer of genetic information between two related genes or DNA sequences (fig. 1).

Gene conversion, first discovered in fungi, manifested as the non-Mendelian segregation of alleles at particular loci in single meioses. In organisms such as yeast, it is possible to recover and analyze all the products of a single meiotic event, an exercise called "tetrad analysis." As meiosis occurs, the chromosomes are replicated to the tetraploid state (two copies of each parental chromosome), followed by two rounds of meiotic divisions resulting in four haploid spores. A typical example of gene conversion revealed by tetrad analysis in *Saccharomyces cerevesiae* is obtained by sporulation of a diploid yeast strain that is heterozygous for a mutation at a selectable locus, such as the auxotrophic marker *HIS4*. The four spores that arise from a single meiotic event can be dissected and inoculated onto culture plates lacking histidine. Under normal Mendelian assumptions, one would expect to see 2:2 segregation at the *HIS4* locus, so two $HIS4^+$ spores should grow, and the other two should remain quiescent. However, in a small percentage of meioses, plating on histidine-negative media will reveal 3:1 segregation in favor of either allele, so three spores may grow instead of two. Nonreciprocal recombination, the genetic event that underlies this surprising finding, represents an alternate outcome of essentially all recombinations. Unifying models of genetic recombination, beginning with the Holliday model and proceeding to the currently accepted double-strand break–repair model, have attempted to account for gene

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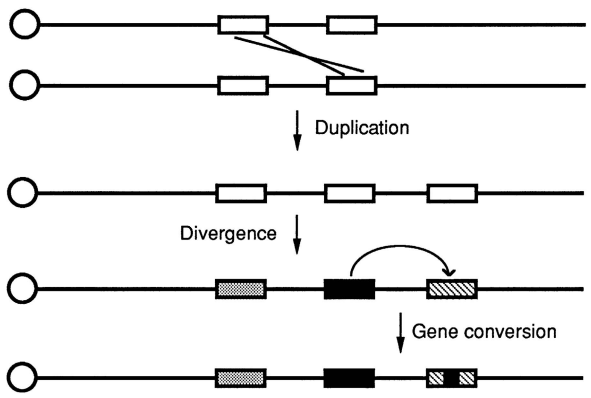


Figure 1 Recombination in the evolution of a gene family. Genes beget other, related genes by means of homologous recombination, a complex event that can take several forms. The process of gene divergence may begin with homologous recombination between two related sequences, shown here as an instance of unequal crossing-over between different gene-family members on homologous chromosomes; it is noteworthy that this type of recombination does not conserve gene copy number. Once extra copies of the gene are established, the individual genes may diverge with time (although this divergence is constrained in many cases; see Liao 1999 [in this issue]), and sequence changes may lead to diversification of function. Finally, gene conversion, a nonreciprocal form of recombination, can cause sequences from one family member to appear in one or more of the others. Gene conversion does not affect gene copy number, but it may cause rapid changes in the degree of diversity among family members.

conversion and its association with crossing-over (reviewed in Orr-Weaver and Szostak 1985).

Gene-family evolution is a balance of several recombinational activities—in particular, unequal reciprocal recombination and gene conversion. The former mechanism can increase or decrease the number of genes in a locally dispersed family, whereas the latter conserves gene-copy number. Like reciprocal recombination, gene conversion can play two roles: On one hand, conversion-mediated sequence homogenization inhibits—and can even reverse—divergence and potential adaptation. Thus, gene conversion between nonallelic sequences can wipe out millions of years of divergence, in a single event. On the other hand, gene conversion can generate diversity by introducing multiple sequence changes into a member of a gene family, creating novel alleles in a single event (Baltimore 1981). A gene conversion–like mechanism appears to be responsible for the generation of new MHC (major histocompatibility complex) alleles in human populations (Kuhner et al. 1991; Parham and Lawlor 1991; Belich et al. 1992). The evolution of a gene family therefore depends on the relative frequencies of reciprocal versus nonreciprocal recombination, the number of genes in a family, preferences in donor/recipient gene-conversion pairs, and the absolute frequency of each in the germ line, compared with point-mutation rates.

There are substantial difficulties facing studies of meiotic recombination in mammals. Foremost is the inability to identify the products of individual meioses. To gain a better understanding of the role of recombination in the evolution of gene families in mammals, it necessary to devise schemes to measure and detect various types of recombination (e.g., inter- and intrachromosomal gene conversion and unequal recombination). With such a system in hand, one can identify genes that influence these processes and can study the effects of parameters such as sequence composition and the allelic states of key recombination genes. On the basis of studies of *S. cerevesiae*, it has been possible to design experiments to address various aspects of recombination in mice and mammalian cells. Below, I outline some of the key approaches that have exploited the special ability to manipulate the mouse genome for the purpose of investigation of unequal recombination in vivo.

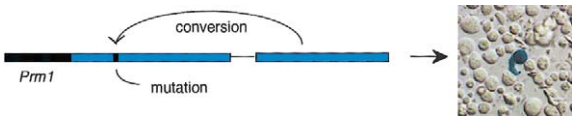
Recombination Readout Systems: Seeing Is Believing

Gene conversion may be assayed in cultured mammalian cells by means of constructs containing duplicated but defective selectable genes, such as thymidine kinase (TK). In this system, restoration of functional TK can occur only by gene conversion from one copy to the other, differently inactivated copy of the gene (Bollag et al. 1989). Intrachromosomal gene-conversion rates as high as 0.5%–0.8% of cells have recorded between duplicated immunoglobulin genes in mouse hybridoma cells (Baker and Read 1995). However, with respect to evolution, the only conversion events of any consequence occur in the germ-cell lineage, either during meiosis or in the precursors of germ cells. To detect potentially rare gene-conversion events in the mammalian germ line, my colleagues and I, as well as others, have screened sperm cells rather than whole animals. One approach involves histochemical detection of transgene reporter activity, whereas the other approach utilizes PCR amplification of particular endogenous loci.

Murti et al. (1992) generated transgenic mice containing a construct designed to measure intrachromosomal gene conversion between defective *lacZ* genes. The construct carried a protamine promoter–driven "recipient" *lacZ* gene, which contained an internal frameshift, as well as a second, "donor" *lacZ* gene, which was truncated at both termini. A gene-conversion event that corrects the mutation in the recipient *lacZ* gene with sequence from the donor would enable the production of functional beta-galactosidase in spermatids, allowing the sperm to stain blue on histology (see sidebar). Blue spermatids have been observed in all transgenic lines, at frequencies as high as 2%, depending on genetic back-

Detection of Germ-Line Gene Conversion in Mice

"Gene conversion" refers to the nonreciprocal exchange of genetic information between two loci. As described in the main text, gene conversion is most easily observed in organisms such as yeast, where the products of an individual meiosis remain physically connected, but the phenomenon is quite general and has been demonstrated in plants and bacteria, as well as in mammals. By formal genetic criteria, it is not possible, in mice or humans, to detect gene-conversion events between alleles on homologous chromosomes. First, such events would be indistinguishable from double crossovers. Furthermore, if gene conversions at loci of interest were rare, it would be exceedingly difficult to raise sufficient progeny to detect convertants, to gain reliable estimates of frequency, or to study the genetic regulation of conversion between homologous chromosomes. However, gene conversion can occur between homologous sequences located anywhere in the genome, not just between alleles. Conversion between recently duplicated, tightly linked copies of a gene is of particular interest for the modeling of molecular evolution (see text and Liao 1999 [in this issue]).



Intrachromosomal conversion between locally duplicated gene-family members is very frequent at some yeast loci and is usually detected by creation of a locus that contains two defective genes side-by-side, followed by selection for revertants. My colleagues and I have used an analogous system for detection of conversion between two defective *lacZ* genes in the mouse germ line (Murti et al. 1992). If the recipient *lacZ* transgene, which is transcribed under a promoter that is active in postmeiotic round and elongated spermatids (protamine-1 [*Prm1*]), is converted by the donor *lacZ* gene, then those sperm harboring the conversion event will stain positively (blue) with the substrate, X-gal. Quantitation can be done either on purified populations of spermatids or by flow cytometry of mature sperm treated with a fluorogenic *lacZ* substrate. The example above shows a *lacZ*-positive elongating spermatid produced by a mouse containing the illustrated transgene construct. The nature of the presumed gene-conversion event is indicated, whereby a "donor" *lacZ* gene (*lacZ* sequences are colored blue) that is truncated at both termini converts a 2-bp frameshift mutation in the *Prm1*-driven "recipient" *lacZ* gene.

ground, and correction of a restriction site in the recipient has been observed after PCR amplification of either bulk sperm or micromanipulated *lacZ*-positive spermatids (Murti et al. 1994*b;* Hanneman et al. 1997). This assay was later adapted to show that ectopic conversion occurs between recipient and donor sequences located on different chromosomes (Murti et al. 1994*a*).

The experiments of Murti et al. have modeled the situation that occurs immediately after a gene-duplication event, when a gene pair shares nearly complete identity. In that system, two genes share 2.5 kb of identity, except for a 2-bp insertion. Since the level of sequence identity is directly related to the frequency of gene conversion, the levels observed in these experiments (2%) might represent the high end of what might occurs outside the laboratory. Because conversion rates as high as 2% are inconsistent with the ability of genes to diverge, it is postulated that recombination must be impaired sufficiently to allow base changes to occur. Once the effect of gene conversion is relaxed, the gradual accumulation of point mutations would further decrease the potential for conversion. Factors that might compromise recombination include disruption of homology (e.g., by sequence deletions or insertions, which would break up long stretches of homology), genetic background factors, or epigenetic mechanisms that promote mutation of duplicated sequences (Kricker et al. 1992).

A modification of the *lacZ* strategy for detection of rare recombination events has been exploited to investigate intrachromosomal recombination between the duplicated human glycophorin genes (*GPA* and *GPB*) in the mouse germ line. In humans, these genes undergo unequal reciprocal recombination at a significant rate. Transgenic mice bearing a construct were developed in which recombination between glycophorin sequences resulted in the juxtaposition of artificial *lacZ* exons. Transcription of this rearranged gene from the protamine 1 promoter resulted in *lacZ* activity in sperm, which was measured by flow-cytometric detection of a fluorogenic substrate. As many of 0.09% fluorescent sperm were detected, suggesting that the properties that make the glycophorin genes recombinogenic in the human germ line are intrinsic to the sequences themselves and are retained in mice (Moynahan et al. 1996).

PCR analysis of sperm has been used to detect and quantify gene-conversion events, in both humans and mice. The advantage of this approach is that endogenous genes are examined. However, these studies have tended to concentrate on significantly diverged genes, and therefore their results probably do not reflect optimal conversion rates between newly duplicated genes. Hogstrand and colleagues examined the conversion frequency of MHC class I genes in mice. Conversion between the nonallelic templates on homologous chromosomes was observed at a rate of ~0.002% (Hogstrand and Bohme 1994). Remarkably, these MHC templates were very small (186 bp) and highly divergent (79% identical to each other). Evidence for gene conversion between HLA class II genes in humans has also been obtained by sperm analysis (Zangenberg et al. 1995). In these studies, ~0.01% of sperm carried a novel allele that was attributable to gene conversion.

Control of Recombination Frequency

Although the influence of DNA sequence homology on gene-conversion frequency is reasonably well under-

stood in mammalian cells (Bollag et al. 1989), relatively little is known about genetic factors and the role that sequence composition plays in various types of recombination. However, there have been increasing data characterizing various *cis* elements or sequence structures that influence recombination frequency in the mouse germ line.

Double Strand Breaks

On the basis of a large body of data from yeast, it has been inferred that a primary sequence determinant that directly induces recombination is that which has a propensity to undergo double strand breaks (DSBs). Such sequences exist naturally in the yeast genome, and they occur at such high levels that they can be directly detected by Southern blotting (the much lower genome size of yeast relative to mammals also facilitates detection). The critical role of DSBs in the initiation of recombination is exemplified in experiments demonstrating that gene-conversion gradients begin at discrete DSBs (Nicolas et al. 1989; Sun et al. 1989). Although no naturally occurring, molecularly detectable germ-line DSB "hot spots" have been identified in mammals, several studies have found that DSBs induced in a locus-specific manner by means of rare-cutting endonucleases such as I-*Sce*I can markedly induce homologous recombination in mammalian cells (Jasin 1996; Elliott et al. 1998; Liang et al. 1998). There is also evidence that DSBs induce gene conversion between *lacZ* substrates in the germ line (P. Romanieko and M. Jasin, personal communication). In yeast, DSB formation is often associated with DNaseI-sensitive sites near promoters, although the frequency of the breaks can be affected by sequences several kilobases away. Since there is evidence for covalent DNA-protein interactions at the site of DSBs in yeast, at least three elements determine the location and frequency of DSBs: local sequence and chromatin structure, *cis* sequences at a distance, and *trans* active protein factors (Liu et al. 1995). Therefore, it is unclear whether, without consideration of the latter two elements, one could predict the likelihood that a given sequence would be recombinogenic.

Recombination Hot Spots and Strain Background Variation

The MHC in mouse contains four regions in which, as a function of physical length, crossing-over has been observed to occur at higher rates than are seen in other regions of the chromosome (reviewed in Lichten and Goldman 1995; Shiroishi et al. 1995). The two best-characterized hot spots have been narrowed to 1–2 kb, and common sequence elements have been observed, although a direct relationship between these elements and the recombination rate has not been established. Interestingly, the MHC hot spots manifest themselves only in certain strain or haplotype combinations. However, although the recombination rates are higher there than at other sites, they are not so frequent as to allow DSBs to be detected by current methods.

The phenomenon of strain-combination dependence of recombination rates is also observed in other regions of the genome, besides the MHC hot spots. At different intervals, crossing-over rates can vary greatly both between males and females and between different strain combinations (Reeves et al. 1990; Heine et al. 1998). There are three possible explanations for this phenomenon: one is that the sequences of the homologous chromosomes autonomously influence the distribution of crossovers; a second is that genetic background governs the distribution; and, finally, it may be a combination of these two. This issue remains unresolved, yet it could potentially provide insight into fundamental recombination mechanisms and their impact on the recombinational activity of gene-family members.

One way to address the question is to exploit a new set of tools that are being developed in mice—that is, consomic strains. These are inbred strains of mice that are homozygous for an entire, single chromosome of a donor strain in a recipient genetic background of a second strain. For example, one could examine whether the distribution of crossovers along a particular chromosome in an F_1 hybrid (say, C57BL/6 X BALB/c) is the same as that in mice in which that chromosome is heterozygous but the rest of the genome is C57BL/6 (such a mouse can be generated by backcrossing a consomic strain bearing the BALB/c chromosome in a C57BL/6 background to C57BL/6). Any differences, in crossover distribution, between the two crosses would indicate that genes in the background influence recombination. In the transgenic experiments that use *lacZ* staining of sperm to detect gene conversion, my colleagues and I have found that conversion rates are far lower in the C57BL/6J inbred-strain background than in the CF_1 strain (Schimenti et al. 1997). It may be possible to exploit this transgenic model—or variations thereof—as a tool either to identify modifiers of recombination in strain backgrounds or to assess the role of particular genes in mice bearing knockouts.

Knockouts

Currently, the most fruitful means of identifying the *trans*-acting factors controlling recombination is to generate mice bearing mutations in the homologues of genes known to play key roles in yeast recombination. Many such proteins, including RecA, topoisomerases, helicases, and ligases, are highly conserved from yeast to mammals. In yeast, many of these genes have been identified in screens for sensitivity to ionizing radiation,

which induces DSBs in chromosomes (Game 1993). This underscores the idea that meiotic recombination evolved from recombinational repair mechanisms active in mitotic cells.

Eukaryotic genes that are related to the *Escherichia coli RecA,* such as the yeast *RAD51* gene, participate in homologous recombination and are of particular interest with respect to the control of gene conversion. RecA promotes strand transfer between homologous DNA molecules in an ATP-dependent manner (Radding 1991; West 1992). Targeted mutagenesis of a meiosis-specific *RecA*-homologue in mice, *Dmc1,* yielded a phenotype similar to that of the yeast gene; meiosis was arrested in prophase, because of the failure of homologous chromosomes to synapse (Pittman et al. 1998; Yoshida et al. 1998). However, this study also underscores the difficulties still posed by the mammalian system: because of meiotic arrest, it was impossible to judge the effect that the *Dmc1* mutation had recombination. In yeast, on the other hand, this analysis was possible, because genetic tricks allow meiosis to be reversed. Thus, sporulating cells can be returned to mitotic growth, and recombination events that occurred prior to arrest can be recovered. Interestingly, the mouse *Rad51* knockout was cell lethal, unlike that in yeast (Tsuzuki et al. 1996). Hence, this mutation was not informative. However, the advent of Cre/LoxP site-specific recombination technology allows the design of conditional mutants, so it should be possible to ablate expression of such genes specifically in certain tissues of interest, including germ cells (Pluck 1996).

With respect to modulation of recombination between duplicated sequences, DNA repair genes may play a role in limiting the interactions between divergent sequences, by imposing strict homology requirements. For example, a knockout of the MutS homologue, the *Msh2* gene, in mouse cells increases *homeologous* recombination (recombination between nonidentical homologues) to levels equivalent to that between identical (isogenic) sequences (de Wind et al. 1995). It has been suggested that DNA repair genes play a critical role in preventing cross-species hybridization and genome stability, by preventing homeologous interactions (Radman et al. 1993).

The Next Step: Mutagenesis Screens for Meiotic Recombination–Defective Mice

As the Human Genome Project has progressed through mapping stages and characterization of expressed genes, the transition to functional genomics has caused a revival of enthusiasm for random mutagenesis in mice. This is because it is widely recognized that mutations are the most powerful tool for understanding the function of a gene in the context of a whole organism. Since mice have proved to be such a valuable model of human development and disease, major mouse-mutagenesis programs are beginning around the world. Most programs are exploiting the germ-line point mutagen ethylnitrosourea (ENU), which is highly efficient at producing mutations in male spermatogonia (Rinchik 1991). Is it possible to identify meiotic recombination mutants in these screens?

In yeast, mutations affecting recombination were isolated in screens for phenotypes such as radiation resistance or failure to sporulate properly. Such screens are feasible because of the ability to replica-plate the mutated cells and to rescue the meiotically arrested cells, and because of the general ease of manipulating a unicellular organism. The development of screens for meiotic recombination–defective mouse mutants faces major obstacles. One problem is that most ENU mutagenesis programs seek to identify dominant mutations in first-generation offspring but that, because they may lead to sterility, many of the mutants of interest may not be recovered in such a screen. An alternative is to conduct "region-specific" two-generation screens in which chromosome deletions are used to identify recessive ENU-induced mutations (Schimenti and Bucan 1998). This approach allows preservation of mutations, via carrier littermates. However, the real problem lies in the development of assays that can reliably and efficiently detect defects in recombination. Some of the transgenic models presented here might play a role in the identification of such mutants.

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