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Resolving Intralocus Sexual Conflict: Genetic Mechanisms and Time Frame

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Abstract

Intralocus sexual conflict occurs due to the expression of sexually antagonistic alleles: those that increase fitness when expressed in one sex but decrease fitness when expressed in the other sex. This genetic conflict is expected whenever the sexes are selected toward differing phenotypic optima for a trait that has a positive genetic correlation between the sexes. Here we synthesize recent developments in the areas of genomics, microarray analysis, and developmental and molecular genetics to establish feasible mechanisms by which the intersexual genetic correlation can be reduced, as well as the time course over which conflict resolution is expected to evolve.

Key words: *genetic correlation, intralocus sexual conflict, microarray, sex-biased gene expression, sexual dimorphism*

Intralocus sexual conflict (IASC) has been documented in a wide variety of traits among many taxa (reviewed in Bedhomme and Chippindale 2007; Bonduriansky and Chenoweth 2008; van Doorn 2009). The genetic foundation for IASC is a strong intersexual genetic correlation for a trait with differing optima between the sexes (Lande 1980). Progress toward resolving IASC requires a breakdown in the intersexual genetic correlation, which is commonly quite strong (e.g., Bonduriansky and Rowe 2005), leading to the evolution of sexual dimorphism. Recent advances in DNA sequencing technology, and the analysis of these sequences, have provided new insights into processes that had previously been viewed, by necessity, as black boxes. One such process is the intersexual genetic correlation. Here, we integrate recent advances in the fields of genomics, microarray analysis, and developmental molecular genetics to evaluate how evolution can resolve IASC and the speed at which this is expected to occur.

Genomic Analysis

One way to resolve IASC is the duplication of a locus experiencing sexually antagonistic (SA) selection followed by the evolution of sex-specific gene expression. Alternatively, a single gene can be spliced, or posttranscriptionally processed, differently in the 2 sexes. All of these processes require differential regulation of a gene in the 2 sexes, that, in turn, can be accomplished when a gene responds differently to some cellular signal(s) of gender. Although there may be other mechanisms to achieve the requisite epistatic interaction between an allele with sex-specific expression and its sex-specific regulator, here we focus on genes that respond in a unique way to sex-specific regulatory substances.

In mammals, the process of sex determination is initiated by a Y-linked gene (*Sry*) that triggers a regulatory cascade, causing the gonads to develop into testes in males and, in the absence of this signal, ovaries in females (Wilhelm et al. 2007). Next, the ovaries or testes release hormones (estrogen and androgen, respectively) that induce sex-specific development, ultimately leading to sexual dimorphism. Sex hormones influence sex-specific gene expression by binding to sex hormone receptors, which then become competent to bind to androgen or estrogen DNA-binding sites. The receptor-bound DNA can both upregulate and downregulate one or more nearby genes (Berger and Watson 1989; Lindberg et al. 2003).

The availability of a complete human genome sequence, coupled with chromatin immunoprecipitation sequencing, which provides the precise mapping of protein–DNA interactions, has recently led to high-confidence estimates for the genome-wide numbers of DNA-binding sites that are targeted by human estrogen and androgen receptors and the ability to verify their regulatory activity on nearby genes. The number of these active estrogen/androgen DNA-binding sites is large. Carroll et al. (2006) estimate that there are 3665 high-affinity DNA-binding sites for the estrogen receptor.

A subsequent study estimates that 1234 of these sites are specifically for the estrogen-α receptor (Lin et al. 2007). A similar study counting the genome-wide androgen receptor DNA-binding sites indicates that these sex-specific regulatory elements are also quite numerous (563; Horie-Inoue et al. 2004), but substantially less common than those for estrogen. Given that the human genome is estimated to contain 20 000–25 000 structural genes (IHGSC 2004), these data suggest that there is the potential for at least a few thousand genes to be regulated in a sex-specific way via sex hormone receptors, but that most genes are probably not under this form of regulation unless the majority of receptor DNA-binding sites regulate multiple genes.

In *Drosophila*, the master regulatory switch controlling sex-specific ontogeny is the gene *Sex Lethal*, the splicing pattern of which (to an active form in females or an inactive form in males) depends on the number of X chromosomes (1 or 2) in a diploid genome (Bell et al. 1991). This gene in turn regulates the splicing pattern of 2 downstream regulators of sexual development: *doublesex (dsx)* and *fruitless (fru)*. Although it is well established that gene products from *dsx* and *fru* must regulate sex-specific gene expression at a large number of downstream genes, to date only 2 genes have been shown to be directly regulated by *dsx*: yolk protein (*yp*; Coschigano and Wensink 1993) and bric-a-brac (*bab*; Williams et al. 2006), and the target genes for *fru* are unknown (Demir and Dickson 2005). Moreover, even though the protein sequence of the DNA-binding domain of the *dsx* gene products is known (Yi and Zarkower 1999), the sequence of its DNA-binding site is unknown. Nonetheless, some DNA sequence(s) that bind *fru* and *dsx* gene products, analogous to the DNA-binding sites of sex hormone receptors in mammals, would seem to be necessary to mediate sex-specific gene expression. In order to determine whether the high potential for sex-specific gene regulation seen in humans (via thousands of DNA-binding sites for androgen and estrogen receptors) is representative of other species, we suggest that similar genome-wide counts of regulatory elements could be made for both the *dsx/fru* system in *Drosophila* and the closely related *mab* system in *Caenorhabditis elegans* (Yi and Zarkower 1999).

These recent studies from genomics and developmental genetics indicate that the evolution of sex-specific gene expression via gene duplication, or alternative splicing, will be a very slow process unless the gene is already under the influence of a sex-specific DNA regulatory binding site, or if a duplicated gene is fortuitously translocated to a location where it obtains such regulation. Evolving new sex-specific regulation via sex hormones or sex-specific regulators (like *dsx* and *fru*) requires 2 complex mutations: one duplicating the gene (or adding an alternative splice site) and the other producing a nearby DNA regulatory sequence capable of responding to a sex-specific cellular signal (like the sex hormone receptor of mammals). Sex-specific posttranscriptional processing of mRNA is an alternative way to achieve sex-specific gene product regulation, but this route would probably also require the evolution of new *cis*-acting regulatory sequences within a transcript that permit the 2 sexes to produce qualitatively different gene products. In contrast, however, genes that are already influenced by nearby sex-specific regulatory elements may require far less complex mutations to achieve sex-specific gene regulation.

Microarray Analysis of Sex-Specific Gene Expression

Despite the large phenotypic differences between males and females found in many species, the majority of genes produce the same transcript in both sexes, suggesting that sexual dimorphism predominantly results from quantitative differences in gene expression (Connallon and Knowles 2005; Rinn and Snyder 2005). Recent studies quantifying mRNA abundances using microarrays have reported a surprisingly high proportion of genes that exhibit sex-specific expression (Jin et al. 2001; Arbeitman et al. 2002; Meikeljohn et al. 2003; Parisi et al. 2003; Ranz et al. 2003; Connallon and Knowles 2005). For example, it has been reported that as much as 57% of genes in both *Drosophila melanogaster* and *Drosophila simulans* show sex-specific levels of expression (Ranz et al. 2003). In these microarray studies, genes that produce more transcripts in males (females) are classified as male-(female-)biased genes.

It has also been reported that sequence divergence among related species is associated with the differences in a gene's expression level between the sexes. For example, Zhang et al. (2004) and Richards et al. (2005) found that sequence divergence in *Drosophila* is higher among sex-biased genes than unbiased genes and that male-biased genes diverge faster than female-biased genes. Divergence in expression level between species is also associated with the sex-biased/unbiased classification of genes (Ranz et al. 2003; Zhang et al. 2004; Richards et al. 2005). For example, changes in sex-biased gene expression account for more than 80% of the gene expression differences between *D. melanogaster* and *D. simulans*, species that diverged approximately 2.5 million years ago (Ranz et al. 2003).

Some authors have argued that since 1) microarray studies indicate that a high proportion of genes exhibit sex-biased gene expression and 2) the level of sex-biased gene expression rapidly evolves among closely related species, these facts collectively indicate that the elimination of IASC may evolve quite rapidly through sex-biased gene expression (e.g., see van Doorn 2009). We think that this conclusion is premature and quite possibly wrong.

Most of the studies on gene expression were conducted using whole organisms, including the gonads. The female ovaries and male testes are highly differentiated organs, so it should not be surprising that large amounts of sex-biased gene expression are detected when these structures are included in microarray analysis. To demonstrate this association between sex-biased genes and gene expression in the gonads, Parisi et al. (2004) used microarrays to compare gene expression levels between male and female *D. melanogaster* with and without the gonads present. After the gonads were removed, less than 3% of somatic genes exhibited sex-biased expression (Parisi et al. 2004; McIntyre et al. 2006). This result suggests that most "sex-biased"

genes simply reflect the fact that ovaries and testes are structurally and functionally very different organs (not surprising, given the manifest differences between sperm and egg) and that the vast majority of genes expressed in the soma are not highly sexually dimorphic in gene expression.

Ellegren and Parsch (2007) have hypothesized that the low levels of sex-specific gene regulation found in the soma of flies might be an artifact of assaying whole animals rather than specific tissues. They argue that if the same genes were upregulated and downregulated in a sex-specific way in different tissues, then these differences may tend to average out when a large number of tissues are combined in a whole-organism assay. To support this hypothesis, they focused on a study that compared gene expression levels of the same somatic organ between male and female mice (Yang et al. 2006). This organ-specific assay detected thousands of sex-biased genes in liver, adipose and muscle tissue, and hundreds of sex-biased genes in the brain. The high degree of sex-biased gene expression in somatic organs supports the conclusion that a substantial proportion of genes expressed in the soma are regulated in a sex-specific manner.

However, upon examining Yang et al.'s (2006) mouse study and the numerous whole carcass studies (with and without gonads), we suggest that it is premature to make any firm conclusions about 1) the proportion of the somatic genome that is sex-biased in gene expression and 2) the rate at which sex-specific gene expression diverges among closely related species. Gene expression is an intrinsically cellular phenomenon that we think cannot be accurately assayed (or compared between sexes or species) when measuring a heterogeneous sample of cell types without controlling the proportion of each. To illustrate this problem, suppose that an organism (or organ) is made up of just 2 somatic cell types: structural (like the fibroblasts of connective tissue) and functional (like the hepatocytes of liver). Further suppose that the 2 cell types have different transcript profiles because of their cell-type specific functions. The genome-wide transcript profile of such an organism will depend on the relative proportions of the 2 types of cells. If males and females differ in these 2 cellular proportions, then sex-biased genes would be detected at many gene loci despite the fact that cellular transcript profiles of each cell type are identical.

Applying this logic to real animals, if males and females differ in size, and if somatic organs do not isometrically scale with body size, a whole-organism assay of transcription would falsely detect sex-biased genes even if cellular transcript levels within each type of cell were identical. Similarly, this result would occur if the sexes had identical body size, but some organs were at least somewhat sexually dimorphic in size. This reasoning can further be applied to the comparison of the same organ between the sexes if the organ, like a muscle or the liver, is sexually dimorphic in any way, for example, in size or the proportion of constituent cell types. Finally, this logic also applies to the comparison of transcript profiles among closely related species that have diverged in body size or the relative size of any organs. However, when the sexes, species, or organs being compared have similar body and organ composition, heterogeneity in cellular composition among samples should be low such that differences in the proportion of diverse cell types have only a minor effect on transcript profiles. Nonetheless, in studies with high statistical power, in which gene expression profiles differing by less that 10–20% can be detected, many false positives may occur. From this perspective, consider the comparison of organ transcript levels between the sexes by Yang et al. (2006). In the liver, they found that 76% of genes displayed statistically significant sex-biased gene expression. However, if they only classified genes as sex-biased when they differed between the sexes by at least a factor of 1.2, then only 13.5% (85% fewer genes) were classified as sex-biased. This result suggests to us that many genes described as sex-biased may be artifacts owing to differences between whole organisms, or organs, in the proportion of different cell types. This problem should be restricted, however, to those loci with low-fold differences detected between the sexes. Until microarray studies are done on homogeneous samples of cells from different sexes/species (or some adjustment is made for heterogeneity of cell types), we think that any estimates of the proportion of sex-biased genes that include low-fold differences may grossly overestimate the number of genes regulated differently between the sexes and the speed at which this may occur.

Evolution of Sex Chromosomes

Another way to alleviate IASC is to move SA alleles, or regulatory elements that influence their expression, to the hemizygous sex chromosome (i.e., Y or W), so that the expression of these genes is limited to the heterogametic sex. However, nonrecombining Y and W chromosomes degrade over time, ultimately becoming functionally degenerate over most of their loci (Charlesworth B and Charlesworth D 2000). For example, the gene content on the Y chromosome accounts for less than 0.2% of the genome of both flies and humans (Lahn and Page 1997; Adams et al. 2000; Carvalho and Clark 2005). With so few functional genes on the Y chromosome, one might not expect it to play an active role in IASC resolution. In spite of this degeneration, the *Drosophila* Y chromosome has been found to substantially influence both the behavior (Stoltenberg and Hirsch 1997; Huttunen and Aspi 2003) and fitness (Chippindale and Rice 2001) of males.

How might the gene-depauperate Y chromosome influence male phenotypes? Lemos et al. (2008) recently demonstrated that polymorphisms at loci on Y chromosomes, taken from a world-wide collection of *D. melanogaster*, influence as many as a thousand genes throughout the genome. Not surprisingly, many of the genes affected by the Y were expressed in the testes. Thus, although the male-limited Y chromosome may be deficient in structural genes, its regulation of many hundreds of genes located on the X and autosomes may provide a simple and powerful mechanism to resolve IASC. Consistent with this idea is the finding that, in both flies and humans, new genes are being recruited to the Y that influence male specific traits (Lahn

and Page 1997; Carvalho and Clark 2005; Koerich et al. 2008).

Although it is now established that the sex-specific Y chromosome can influence gene expression on the X and autosomes, we do not think that the presence of Y or W chromosomes will strongly influence the rate at which IASC is resolved via the breakdown of the intersexual genetic correlation. To up- or downregulate specific genes, the Y or W must be able to produce a regulatory signal (like a micro-RNA or a transcription factor) that specifically targets the transcription rate of some genes (like those under SA selection) but not others. This would seem to require the evolution of an unambiguous regulatory element near to the influenced genes (or the requisite epistasis must be produced by some other, still unknown, process). If this were the case, then we would expect the regulation by Y-or W-specific genes to evolve at a rate similar to that of estrogen- and androgen-regulated genes.

Discussion

Recent advances in genomics, microarray analysis, and developmental biology suggest to us that the speed with which IASC is resolved will fall into 2 categories: fast and slow. The fast result will occur for traits in which at least some of the controlling genes are already regulated by 1) a sex hormone receptor, 2) sex-specific transcription regulators like *dsx*, *fru*, and *mab*, or 3) a Y-or W-linked transcription regulator. In this case, the genetic architecture necessary for sex-specific gene expression/regulation is already extant and it only needs to be quantitatively modified. The slow result will occur for traits that are controlled by genes lacking pre-existing sex-specific expression/regulation. If we use, as a guide, the ratio of the number of DNA-binding sites for sex hormone receptors (4228) to the total number of genes in humans (~25 000), we would predict that most traits will fall into the "slow" category, unless many genes are regulated, on average, by each DNA-binding site. In contrast to this prediction, some authors have used recent results from microarray studies to conclude that sex-specific gene regulation is already present at most gene loci and that quantitative changes in gene expression between the sexes can rapidly evolve (i.e., can rapidly diverge between close congeners). This would imply that resolution of IASC could occur rapidly for most traits and genes. We think that this conclusion is premature for 2 reasons. First, in whole-organism studies, like nearly all of the *Drosophila* work, most sex-biased gene expression is attributable to the presence of ovaries versus testes, with the expression level of genes in the soma being largely sexually monomorphic. Second, in organ-level studies, most sex-biased genes may be artifacts that are expected to arise when organs from males and females have even small differences in their proportion of different cell types.

One of the surprises from the genomic analysis of DNA-binding sites for androgen and estrogen receptors was a nearly 7-fold higher number of sites for estrogen than androgen. A simple hypothesis for this disparity is that the operation of stronger sexual selection in males makes the intensity of net natural selection higher in males compared with females. If this were the case, selection on SA alleles would more commonly lead to the fixation of the male-benefit allele (Gavrilets and Rice 2006). Therefore, in order to ameliorate their reduction in fitness due to the fixation of male-benefit alleles, females would experience stronger selection to accumulate new DNA-binding sites for estrogen receptors, compared with selection for new androgen receptors in males.

A second surprise from our literature review was the finding by Lemos et al. (2008) that up to a thousand genes have their expression level influenced by polymorphisms on the *D. melanogaster* Y chromosome. Because this chromosome has very few structural genes (only 12 are currently known, reviewed in Carvalho et al. 2009), it is remarkable that such a coding gene "David" can function as such a regulatory "Goliath." Experiments designed to understand how the Y regulates genes on the X and autosomes may provide new mechanisms by which sex-biased gene expression is achieved.

The biggest surprise from our review of the literature, however, was the near complete lack of recent experimental studies in which artificial disruptive selection was applied to specifically reduce the intersexual genetic correlation for a trait. Recently, Zwaan et al. (2008) applied disruptive selection on development time in the butterfly *Bicyclus anynana* and found that after a short period of time (8 generations) there was no detectable change in development time dimorphism, but after a longer time (33 generations), they did see an increase in sexual dimorphism in one of their treatments. Additionally, there are a small number of older experimental studies that attempted to change the amount of sexual dimorphism for shared traits and report mixed results. For example, Bird and Schaffer (1972) applied artificial selection for 15 generations on pre-existing sexual dimorphism for wing size (measured by the length of the third longitudinal wing vein) in a *D. melanogaster* laboratory population. This cumulative SA selection changed the level of pre-existing sexual dimorphism by 15% in the direction already extant in the population (larger wings in females) and 50% in the other direction. In contrast, Harrison (1953) failed to observe any changes in sexual dimorphism for abdominal chaetae (bristles) after 17 generations of divergent selection between the sexes was applied in *D. melanogaster*. Given the small number of such studies, it is not clear how general these results may be. There are some additional studies that do report changes in sexual dimorphism for various traits that have occurred during selection experiments. In these studies, however, either the trait with the observed change in sexual dimorphism was not the trait that was under direct selection (Reeve and Fairbairn 1999; Rundle et al. 2005; Chenoweth et al. 2007; Kwan et al. 2008) or the experimental protocol did not place the trait under divergent selection between the sexes (i.e., there was positive or negative selection in one sex, with no selection on the other; Reeve and Fairbairn 1996). In these studies, it is difficult to make concrete

conclusions because the observed changes in sexual dimorphism might not have occurred if the traits in question experienced divergent selection between the sexes. Although recent genomic and molecular studies can be used to make educated guesses about the opportunity for IASC resolution, there is a clear need for more direct experimental studies to determine how rapidly SA selection can lead to a reduced intersexual genetic correlation.

In summary, our review of recent advances in genomics, microarray analysis, and developmental molecular genetics suggest that some forms of IASC may be rapidly resolved (those that are already associated with sex-specific regulatory pathways) whereas others, possibly most, may persist for long periods of evolutionary time. Our conclusions are necessarily tentative, however, because newly implicated genetic mechanisms to resolve IASC, such as genomic imprinting (Day and Bonduriansky 2004), may provide important alternative forms of resolution. Ultimately, however, only a diverse set of studies using experimental evolution will give us a clear answer to the speed at which most forms of IASC are resolved.

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