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Intralocus sexual conflict resolved through gene duplication

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Gene duplication is mainly recognized by its primary role in the origin of new genes and functions. However, the idea that gene duplication can be a central player in resolving sexual genetic conflicts through its potential to generate sex-biased and sex-specifically expressed genes, has been almost entirely overlooked. We review recent data and theory that support gene duplication as a theoretically predicted and experimentally supported means of resolving intralocus sexual antagonism. We believe that this role is probably the consequence of sexual conflict for housekeeping genes that are required in males and females, and which are expressed in sexually dimorphic tissues (i.e. where sexually antagonistic selection is exerted). We think that these genes cannot evolve tissue-specific expression unless they duplicate.

Intralocus sexual antagonism drives genome evolution

In species with two sexes, a single genome encodes for two different organisms, males and females, and a large portion of the genes are expressed in both sexes [1]. However, given the ecological, developmental, morphological, physiological, and reproductive differences between sexes, males and females are under distinct selective regimes [2,3]. Hence, the genome that can make well-fitted females is often the one that makes unfitted males [4]. This last observation reveals the existence of intralocus sexually antagonistic variation (i.e. the existence of alleles of genes selected in opposite directions in males and females). This type of variation can drive fast genomic changes [5–8]. Notably, intralocus sexually antagonistic variation might be even more prevalent in genomes with heteromorphic sex chromosomes [5,9,10] and it should continue to shape genomes in different ways in those genomes. For instance (as we argue below), recent data suggest that sex-specific duplicated genes might often be selected in those genomes to resolve intralocus sexually antagonistic conflicts. We present a detailed model of how this might occur and propose ways to explicitly test the model.

Testis- and sperm-specific gene duplicates: the data

A compilation of examples reveals that a non-random set of genes are being duplicated recurrently some of the time, are evolving testis-specific expression by means of duplication into a new genomic location, and are often evolving under recurrent positive selection or becoming specialized. We argue that these data support the idea that intralocus sexual antagonism is being resolved through gene duplication and are consistent with the testis being one of the most sexually antagonistic tissues.

A first, very compelling example is the observation that 83% of the nuclearly encoded mitochondrial genes that are relocated exhibit testis-specific expression, a pattern that is not shared by the respective parental genes [11]. Significantly, most of these duplicated genes are X-to-autosome or autosome-to-autosome copies and encode for proteins with energy-production functions, whereas nuclear genes encoding for other mitochondrial functions (e.g. transcription, translation, biosynthesis) remain in the genome mostly as single, broadly expressed, copies [11]. Gallach et al. [11] suggested that, because sperm have a short lifespan and do not transfer their mitochondria to the next generation [12], natural selection might favor males who produce large amounts of sperm (or fast sperm) despite the high

Glossary

Intralocus sexual antagonism: conflict that occurs if alleles of a gene (locus) encoding different isoforms are selected in opposite directions in males and in females.
Tissue antagonism: conflict that occurs if alleles of a gene (locus) encoding different isoforms have different effects in different tissues (i.e. the allele that functions better in a tissue is the allele that performs the worst in another tissue and *vice versa*). Tissue antagonism can lead to sexual antagonism if the tissue-specific advantage translates also in a sex-specific advantage.
Gene duplication: a process that leads to additional copies of genes in the genomes; it can be DNA- or RNA-mediated if the mechanism involves only DNA or involves RNA, respectively
Paralogs: genes that originated through gene duplication.
Retroduplication: RNA-mediated duplication; duplication mechanism that involves the retrotranscription of an mRNA and insertion in the genome.
Retrogene: gene that originated through retroduplication.
Sperm individualization: process that leads to the formation of individual sperm cells from previously interconnected spermatides via cytoplasmic bridges.
Relocation: event of gene duplication to a different genomic location while the parental gene is preserved; it can be DNA- or RNA-mediated.
Bidirectional regulatory regions: regulatory regions that can drive expression of flanking genes in both directions.
Meiotic sex chromosome inactivation (MSCI): premature inactivation of the sex chromosome during meiosis in the germline of the heterogametic sex (XY males and ZW females).
Subfunctionalization: neutral partition of the broad pattern of expression of a gene in two genes after gene duplication.
Dosage compensation (DC): regulatory mechanism of the gene expression used in many XY organisms to achieve the same transcriptional level of the X-linked genes between sexes despite the presence of different numbers of sex chromosomes in males (XY) and females (XX).
Hemizygosity: state of the X or Z chromosome in the heterogametic sex characterized by the presence of only one copy of the genes in that chromosome and by the recessive effects of those genes being exposed to selection.
Chromosome residency: time that a chromosome spends in males or females, which is the same in the case of autosomes. Conversely, sex chromosomes (i.e. X and Z) spend twice as much time in the homogametic (i.e. XX and ZZ) than in the heterogametic sex (XY and ZW).

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0169-5347/$ – see front matter doi:10.1016/j.tree.2011.02.004 Trends in Ecology and Evolution, May 2011, Vol. 26, No. 5

mutation rate that might be associated with high-energy production [13]. Therefore, even though it could be beneficial to decrease the mutation rate in other tissues (i.e. soma or ovary) by preventing the formation of reactive molecules, in the case of sperm, more benefit may be obtained by producing a lot of energy for fertilization despite the mutations associated with this. This situation would generate a conflict among tissues ("tissue antagonism"; Box 1) under which a certain allelic variant beneficial to a particular tissue(s) (e.g. the testis) would increase the fitness of some individuals (males carrying this allele) despite the detrimental effects in other tissues (somatic tissues or ovary). In agreement with this idea, Gallach et al. [11] concluded that mitochondria with high rates of energy production could be essential for male competition but detrimental in females, leading to intralocus sexually antagonistic selection [2]. In addition, Gallach et al. proposed that the observed testis-specific paralogs lead to the resolution of this intralocus sexual antagonism [11]. Some of these paralogs (*CG18418* and *CG6255*) have been evolving under positive selection [14] revealing that selection for a different function of these genes in the testis is being exerted.

Similarly, in mammals, glycolytic enzymes are also known to have testis-specific paralogs (*Pgk2* retrogene, *Gapdhs, Ldhc,* and two, *Aldoart1* and *Aldoart2, Aldolase* retrogenes) [18]. It has been suggested that unique characteristics of the enzymes encoded by these paralogs might be required to localize along the sperm tail [19] to increase the stability of the enzyme until fertilization and/or for sperm metabolism [18]. Interestingly, while purifying selection was inferred to act on *Aldoart1* and *Aldoart2* protein active sites, positive selection and convergent amino-acid substitutions in both enzymes were detected at many other sites [20]. It is mainly glycolytic enzymes

Box 1. Intralocus sexual antagonism resolved through gene duplication: a model with strong positive selection at every step

Here, we introduce a model that depicts a gene that begins to segregate for sexually antagonistic alleles as a consequence of the antagonistic effects of the new allele on different tissues. The resolution of this conflict through time by gene duplication is outlined.

Gene A is initially monomorphic (only allele A1 is present; Figure I) and bestows the same fitness to every cell type in both sexes (time 0, rows A and B). A mutation in the protein-coding region of the gene creates a new allele (allele A2) encoding for a protein variant that increases fitness in the testis, with a cost in the soma and ovary (time 1, row A). Natural selection acts at the individual level so, if the cost in the soma is not very high, A2 might be a better allele for males than A1, but it will come with a cost for females (time 1, row B). This new allele causes a conflict between tissues, as well as a conflict between the sexes. We do not depict the exact effects of the alleles, nor do we depict their chromosomal location or the dominance of the alleles (see Box 2). We only illustrate that, in general, the effect of A2 is dependent upon the sex and that A2 is a better allele for males and comes with a cost for females. Once the antagonistic allele begins segregating (A2), selection will favor its duplication and relocation (i.e. testis-specific expression and differentiation). Situations analogous to this have been modeled before for cases of heterozygote advantage [15,16], and it has been emphasized that allelic divergence is expected to promote gene duplication [15]. In addition, the feasibility of this model increases if we consider that the rate at which new gene duplications are introduced every generation is now known to be very high, as revealed by new genomic data [17]. Whenever allele A2 duplicates creating a new gene (gene B) and evolves testis-specific expression (time 2, row A), selection will favor the individuals (males and females) bearing the combination of A1B (time 2, row B). This situation will lead to the fixation of allele A1 (gene A) and duplicated gene B, resolving the sexually antagonistic conflict (time 3, rows A and B). The outcome will be the presence of the old housekeeping gene (gene A) and a new tissue-specific gene (gene B) as observed in the presented data.

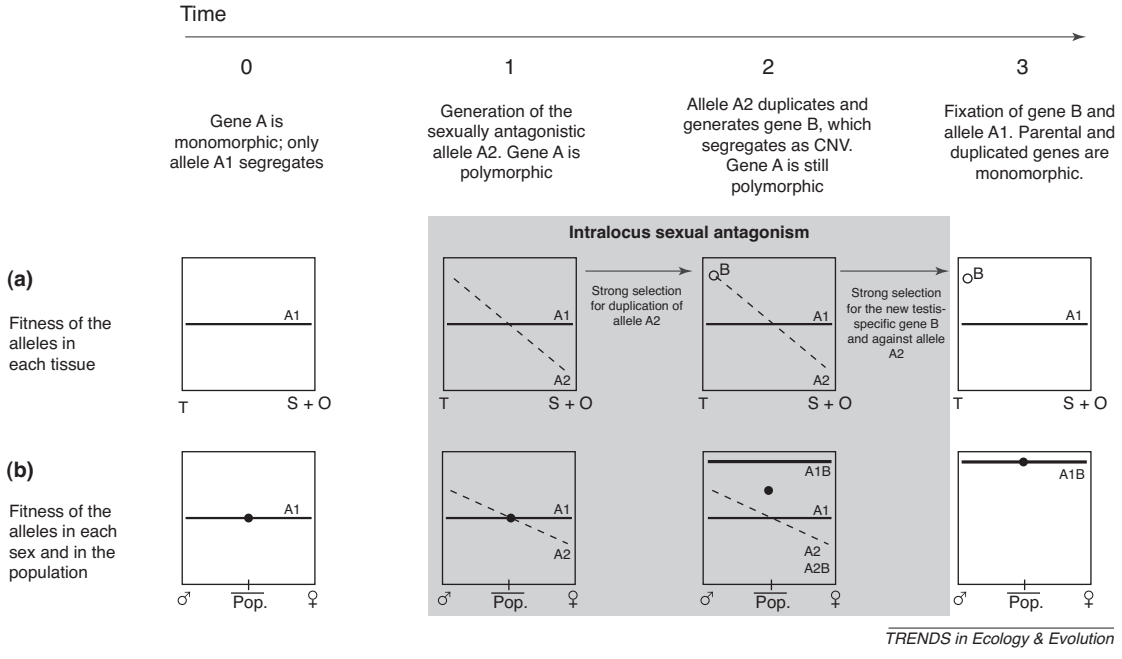

Figure I. The process of intralocus sexual antagonism resolved through gene duplication is shown. The columns reflect four consecutive events in time while the rows reflect the fitness of the alleles in the tissues (row A) and in the sexes and population (row B). T: fitness of the alleles in testis. S + O: fitness of the alleles in somatic tissues of both sexes and in the ovaries. Pop.: population. Black dot: fitness of the population as a rough estimate of the average fitness between both sexes. White dot: fitness of the duplicated gene B in testis. Note that no line can be represented for the fitness of gene B since gene B is not expressed in somatic tissues or the ovary. Before fixation, gene B segregates as a copy number variant (CNV). Framed in gray, we depict the time gene A is segregating the antagonistic allele.

distributed along the longest segment of the flagellum of mammalian sperm rather than mitochondrial metabolism that contribute most of the ATP needed for sperm motility [18]. We again conjecture that the need for sperm-specific functions probably leads to intralocus sexual antagonism, and that gene duplication might allow the resolution of this sexual conflict. Interestingly, *Pgk2* has been recurrently retroduplicated [21], arguing in favor of the strength of these selective pressures. *Pgk2* is an X-to-autosome copy, but these duplicated glycolytic enzymes are X-to-autosome and also autosome-to-autosome copies.

Another interesting example involves the *Drosophila* proteasome (a protein complex involved in protein degradation). In *Drosophila melanogaster*, 36% (i.e. 12 of 33) of the genes encoding for the 26S proteasome subunit have been observed to undergo multiple relocations (DNA- and RNA-mediated) and further independent evolution of testis-specific expression [22]. Again, these duplicated genes are not only X-to-autosome, but also copies in other directions. The authors of this report argue that a fraction of these genes are probably specialized proteasome proteins for sperm individualization [22].

Recent studies show that two nuclear transport proteins (*Dntf-2* and *Ran* [23]) have been recurrently retroduplicated to produce testis-biased genes that have evolved under recurrent positive selection [24]. Male germline conflicts related to sexual selection, segregation distortion, and/or parasite-related conflicts [24–26] have been proposed to explain the recurrent fixation, positive selection and losses of some of these genes in some lineages [24]. This example reveals a potential additional source for sexual antagonism. Hence, for genes involved in male germline conflicts (possibly *Dntf-2* and/or *Ran*), natural selection might favor different alleles for males and females. Gene duplication and sex-specific expression of the male beneficial allele would again resolve this sexual antagonism ([24] and Box 1).

Interestingly, relocation (DNA- and RNA-mediated) seems to be repeatedly involved in the examples given above and in acquiring testis-specific expression [11,27–29]. How relocation favors the evolution of this tissue-specific pattern of expression has been partially answered [29–32]. Insertional biases and a correlation between being expressed in the testis and proximity to testis-expressed genes have been proposed. However, although there are testis-expression domains in *Drosophila* [33] that are probably controlled through different modifications in the structure of the chromatin in testis and somatic tissues [34], it is unclear how much the chromatin context or bidirectional regulatory regions [32] contribute to these effects. In some instances, the evolution of testis-specific regulatory regions might need to be invoked [30]. In addition, acquiring tissue-specific expression would reduce the pleiotropic constraints over the sex-biased gene [35] and relocation would release the gene from genome-wide sequence homogenizing forces such as gene conversion [36], thereby facilitating the evolution of new functions of the relocated sex-specific genes.

We argue that the plethora of testis-specific copies of housekeeping genes that have specialized or are under recurrent positive selection (including duplicates of the TATA-binding protein associated factors, or TAFs, or of telomere capping proteins) [28,37–42] might have frequently originated by gene duplication to resolve intralocus sexual conflicts. In agreement with our model, data indicate that male-biased genes originate more frequently via gene duplication than non-biased or female-biased genes [37,41,43,44]. This suggests that gene duplication is particularly involved in the evolution of new male-biased genes. Interestingly, a big fraction of those male-biased gene duplications are testis-specific duplicates of broadly expressed genes [45].

We propose that intralocus sexual antagonism often begins in the parental gene via male selection for an allele (i.e. a sexually antagonistic allele) that performs better in the testis but worse in other tissues (i.e. male and female soma and ovaries) and culminates with fixation of a relocated specialized male-specific gene (Boxes 1 and 2). We do not think that meiotic sex chromosome inactivation (MSCI; [46]), subfunctionalization [47] or selection for higher expression (given that males carry only one X chromosome and need to dosage compensate [48]) can completely explain the data introduced above. Hence, the MSCI hypothesis (which states that autosomal duplicated genes will be favored if they express in the male germline because they provide an active copy of the gene inactivated by MSCI [27]) cannot explain why there are so many autosome-to-autosome duplications. Also, subfunctionalization does not explain why the partition of expression is always testis *vs.* all other tissues or even the enrichment and recurrent duplications for certain functions. The need for dosage

Box 2. Intralocus sexual antagonism resolved by gene duplication: supporting data for the model, and predictions

Our duplicative model proposes that intralocus sexual antagonism can be resolved by gene duplication (Box 1). The conditions under which the antagonistic allele will increase in frequency and for how long it will segregate in the population have been studied in detail by other authors [10,49] and are dependent upon the chromosomal location, the fitness effects and the dominance of the segregating alleles. Importantly, Fry [49] recently discussed the literature and conditions for the maintenance of polymorphism under intralocus sexual antagonism. He concluded that, under equal dominance between sexes, the conditions for the maintenance of polymorphism are more restrictive for autosomes, which was in agreement with the conclusions of Rice [10]. However, if dominance is sex-dependent, partial dominance of A2 (Box 1) in males and of A1 (Box 1) in females can maintain polymorphism for a broad set of selection coefficients for autosomes. In conclusion, these studies showed that sexual antagonism could maintain intralocus variation in the X chromosome and autosomes (Box 3).

The predictions of this model are several and can be tested: (i) sexual antagonistic variation should map to housekeeping genes even if they have already produced a sex-specific gene (Box 3), and (ii) the study of the function of the duplicated (e.g. testis-specific) genes should reveal a new or specialized function. Interestingly, in organisms with ZW sex-determining systems, the heterogametic sex (i.e. females ZW) does not have dosage compensation [50] but has MSCI [51]. If, as we propose, the testis is the most sexually antagonistic tissue, we should find a high number of relocations, particularly (although not exclusively) Z-to-autosome relocations of male-biased and male-specific duplicated genes. An excess of an out-of-the-X pattern of female-biased genes would give support to the MSCI. Therefore, analyzing the genome of ZW organisms may be particularly useful to test not only our model, but also the MSCI model.

compensation (DC) cannot explain autosome-to-autosome relocation patterns or just the mean level of expression of the parental X-borne genes [11]. Finally, selection for higher expression alone does not explain why duplicated genes often seem to be under recurrent positive selection or become specialized.

Sexual antagonism and sex-biased expression

The resolution of intralocus sexual antagonism is believed to occur through the evolution of sex-biased expression [10]. In his classic study, Rice demonstrated that, given the hemizygosity in males and longer X chromosome residency in females than in males (2/3 *vs.* 1/3), both sexes could bring to high frequency new sexually antagonistic alleles despite the harm on the other sex [10]. Males could increase the frequency of sexually antagonistic alleles that are recessive and beneficial to males whereas females could similarly increase the frequency of sexually antagonistic alleles that are dominant and beneficial to females. This chromosome would, therefore, harbor most intralocus sexually antagonistic variation. Rice also suggested that this intralocus sexual 'battle' would be resolved through the evolution of modifiers of expression that would lower the expression of the particular gene in the harmed sex (i.e. through the origin of a sexually dimorphic trait; Box 3) [10]. However, this idea is controversial for several reasons. First, intralocus sexual conflict does not seem to be resolved, but rather to persist [52]. Second, most sex-biased expression (particularly male-biased expression) does not appear to evolve by decreasing the expression level in one of the sexes [48,53]. Third, the chromosomes that contain most of the sexually antagonistic variation (e.g. X chromosome; [9,10,54]) would be predicted to accumulate sex-biased genes, and this is not always true [55–57]. In addition, it has been overlooked that many sexually antagonistic genes might be needed by both sexes, and losing the expression of the gene in one sex is not feasible.

Rice's model might apply to genes that can lose or decrease expression in one sex (i.e. sex-specific 'dispensable' genes). However, the conflict might instead be resolved as we suggest above through duplication of the antagonistic allele in other instances (see Box 3 for

Box 3. Comparison of the resolution of intralocus sexual antagonism through evolution of modifiers of expression and through gene duplication

Widely expressed (i.e. housekeeping) genes (black lines; Figure I) undertaking basic cellular tasks can be located on the X chromosome or on autosomes. At some point, an antagonistic allelic variant of a housekeeping gene will appear. This gene will segregate an allele with the original protein function (black dot) and another one with the new antagonistic protein function (blue dot for male-beneficial/female-detrimental allele, and pink dot for female-beneficial/male-detrimental allele). Theoretically, a large number of antagonistic alleles will increase in frequency over time and remain polymorphic in the population if located on the X chromosome, whereas this is much more improbable if they are located on autosomes (see Box 2 for details). Under the classic model, the antagonism will be resolved through the evolution of modifiers of expression that will favor sex-biased, and optimally, sex-specific expression (blue and pink lines, for male- and female-biased genes, respectively). Under the duplicative model, the antagonistic allele will duplicate into another chromosomal position, favoring sex-specific expression of the duplicated allele and the fixation of both genes in the population, leading to resolution of the sexual antagonism (see Box 1 and Figure I). For this model, two additional features are depicted: (i) sexually antagonistic variation on autosomal genes may also be resolved through duplication of the sexually antagonistic allele and acquisition of sex-biased expression; and (ii) because parental genes keep their function and broad expression pattern, a new antagonistic allele (sky-blue dot) may appear. This therefore explains the persistence of the intralocus sexual antagonism, and recurrent duplication can be found (sky-blue line).

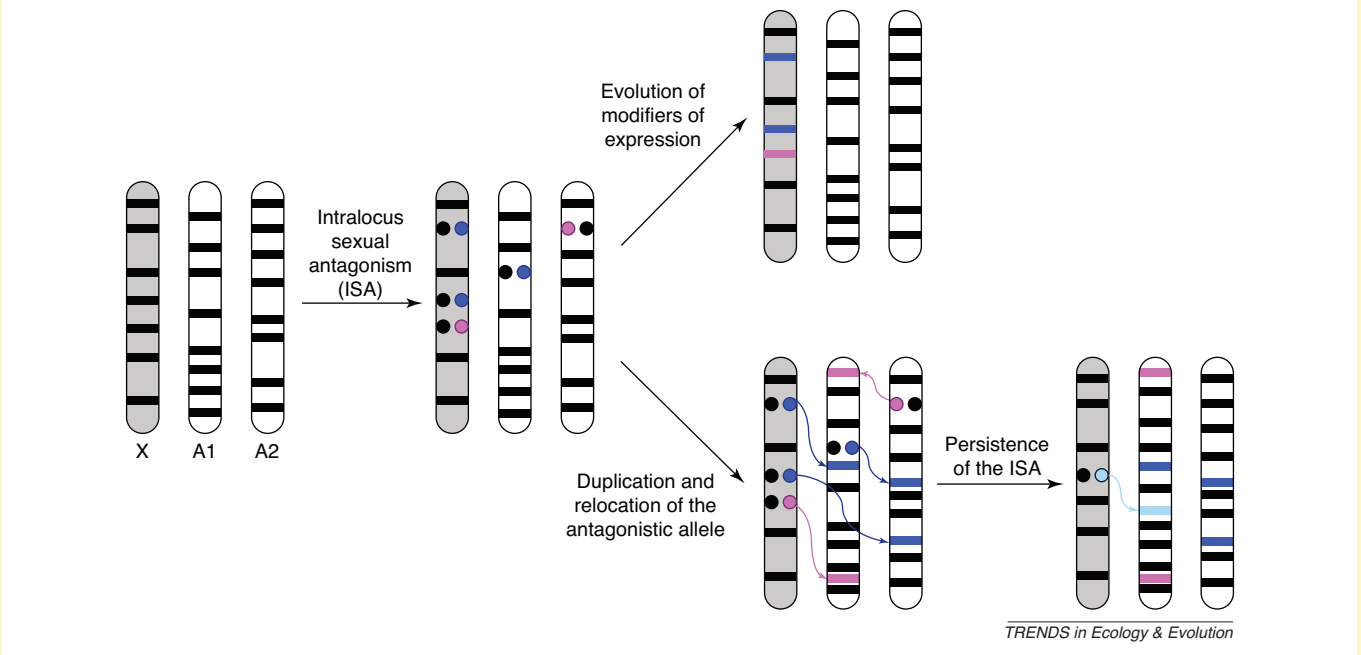

Figure I. Illustration of two modes of resolution of intralocus sexual antagonism: evolution of modifiers of expression (upper side) and gene duplication (lower side). For simplicity, only the haploid set of chromosomes representing one X chromosome (gray bar) and two autosomes (white bar) are shown.

differences between the classic model and our model). Other models that include gene duplication have been suggested to resolve sexual antagonism, but all of these models involve the creation of a male and a female gene [2,3,58,59]. In one of these models [59], gene duplication has been even proposed to explain MSCI, but does not account for the continuous duplication of genes after the heteromorphic sex chromosomes and MSCI have evolved, or for duplications from autosome to autosome. Our hypothesis predicts an excess of X-to-autosome duplications for sexually antagonistic genes but, in addition, because many housekeeping genes are located on autosomes, we also predict autosome-to-autosome duplications of sexually antagonistic genes (Box 2 and 3). In consequence, our model may explain many gene-duplication cases for which MSCI, or level of expression limitations (i.e. DC) are not satisfactory. The proposed model might be the best explanation for gene-duplication patterns, particularly if other hypotheses, such as MSCI [46], subfunctionalization [47] or DC [48], cannot satisfactorily explain the observed data. We do not think that our hypothesis replaces other hypotheses, but instead might complement them.

In the following section, we briefly introduce why we think that tissue sexual identity (i.e. the fact that some sex-determination cascades are triggered only in particular tissues) and sexual antagonism are intimately related biological phenomena.

Tissue dimorphism, sex determination and sexually antagonistic conflict

Data from *Drosophila* suggest that sex-biased expression is mostly due to shifts in particular tissues (largely testis-specific genes [41]), instead of shifts in expression that affect the whole body. Why do only some tissues contribute to sex-biased expression? In *Drosophila*, the ratio of X chromosomes to autosomes determines the absence or presence of the *Sex lethal* (*Sxl*) protein. In the absence of *Sxl* protein, the DC system is activated. In parallel, *Sxl* also triggers male- or female-specific pathways ending in sex-specific isoforms of the *doublesex* (*dsx*) and *fruitless* (*fru*) proteins that confer sexual identity to male and female cells [60,61]. Interestingly, however, not all tissues express *dsx* or *fru*, so that, although most cells 'know' how many X chromosomes they have, not all of them can translate the X chromosome number into sexual identity. Robinett et al. [61] recently showed that *dsx* is expressed in almost all of the cells of only a few tissues (genitalia, brain and central nervous system, and fat body), but in only a few or no cells in the other tissues. In other words, only these tissues as a whole, 'know' their sexual identity.

We suggest that sexual antagonism may appear in tissues with or without *dsx* or *fru* expression, but it will be resolved in those tissues that are already transcribing these genes (i.e. sexually differentiated) or that will eventually recruit these pathways. The overlap between tissues exhibiting sex-biased or sex-specific expression and *dsx* or *fru* expression makes perfect biological sense because the tissue first needs to trigger a sex-specific cascade to later transcribe a sex-specific gene. In other words, for a tissue to express a gene male (female)-specifically, it must first know it is a male (female) tissue. Therefore, we think that sex-determination pathways are relevant to understand both the advent and the resolution of sexually antagonistic conflicts.

The testis is a tissue in which these sex-determination pathways are triggered, and is very different from other tissues. The testis must make sperm, and it is under strong selective pressures from sexual selection, parasite-related conflicts and segregation distortion to specialize and evolve quickly. Therefore, the testis probably generates most of the antagonistic conflicts among tissues [59]. Hence, it is probably the most sexually antagonistic tissue, which explains the number of sex-biased genes expressed there and the number of duplicated genes. Control of parasite-related conflicts and segregation distortion will also occur in ovaries and this might exert strong selection in testis and ovaries, but sexual selection might be stronger in males [37,62], and is likely to lead to stronger selection and tissue antagonism in testes than in ovaries.

Conclusions and further analyses

In this review, we propose a model and introduce some available experimental data suggesting that gene duplication can act as a resolution mechanism for intralocus sexual conflict. Consistent with the possibility that these new duplicated genes resolve sexual conflicts, most of them exhibit sex-specific functions. Additionally, most of these genes not only have sex-specific, but also tissue-specific, functions. Interestingly, only a few tissues have the potential to establish a sexual cellular identity in *Drosophila*, and only those tissues will be able to evolve sex-biased or sex-specific expression. We suggest that these tissues, in particular the testis, are the source of sexually antagonistic conflict and also the place where the conflict will be resolved, thereby leading to tissue-specific expression.

Several predictions emerge from the data, the model and our views presented in this article. We observe many housekeeping genes being duplicated and evolving testis-specific expression. We predict that much of the sexually antagonistic variation will map to genes that are housekeeping genes involved in conflicts that do not have a sex-specific duplicate. However, this prediction remains to be tested. In addition, if sexually antagonistic conflicts are resolved through relocated sex-specific duplicates, then antagonistic variation will often map to a different location than sex-biased expression, and the location of sex-biased expression will not be a good predictor of the location of sexually antagonistic genes (Box 3). This is in agreement with recent results [54] and in contrast with previous models and assumptions [10,63,64].

Theoretically, the X chromosome and autosomes can support antagonistic variation (Box 2). However, the data seem to indicate that, in *Drosophila*, a higher proportion of antagonistic variation maps to the X chromosome [9,54]. Under our model and hypothesis regarding which tissues contribute most to the antagonism, the conflict will often be resolved through duplication of the antagonistic allele and evolution of testis-specific expression of the duplicate. Because the X chromosome holds most antagonistic alleles, most relocated genes will be generated from the X chromosome, helping to explain the autosomal location of male-biased genes and the out-of-the-X pattern [27,65].

According to our model, the initial sexual antagonism is erased after the duplication of the antagonistic allele, making this model difficult to prove. However, some predictions can be tested, as mentioned above (see also Box 2). What proportion of sexually antagonistic conflict is resolved through gene duplication remains to be determined, and this will not be easy to estimate. Yet, given the number of male-specific duplicated genes ([24,37–39,41]; Box 2) and their features (i.e. a non-random set of genes are duplicated sometimes recurrently and often from autosome to autosome, evolving testis-specific expression, often evolving under recurrent positive selection or becoming specialized and eventually being lost sometimes), it would seem that a significant part of gene duplications occur to resolve sexual conflicts. Importantly, a large part of the intralocus sexual antagonism is probably driven by recurrent selective pressures in the male germline (sexual selection, parasite-related conflicts and segregation distortion), and hence the intralocus sexual conflict emerging from these conflicts might be resolved only transitorily (Box 3), explaining its persistence [52] and leading to the rapid turnover of male-specific duplicates [24] and male-biased expression [37,41]. Therefore, observations made at a particular point in time probably represent an underestimation of how often intralocus sexual antagonism is resolved through gene duplication.

Acknowledgements

We would like to thank Jeff Demuth, Bill Rice, three anonymous reviewers for reading this work and providing feedback, and Jennifer Gage for proofreading the manuscript. This research was supported by UTA startup funds and grant GM071813 from the National Institutes of Health, USA, to Esther Betrán.

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