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NEWS AND COMMENTARY

Gene expression

Fast males

B Oliver

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It is becoming increasingly clear that much of what makes one species different from another is not a different set of protein-encoding genes, but variation in how those genes are deployed in a regulatory network. That sexually dimorphic features and the underlying coding sequences evolve more rapidly than those associated with more mundane functions is reasonably well established (Singh and Kulathinal, 2000). Evolutionary biologists are now using microarrays to study global sex-biased gene expression, which until recently has been beyond experimental reach. An excellent example of this is a recent paper by Meiklejohn *et al* (2003), which explores sex-differential gene expression in *Drosophila melanogaster* and reports that genes with male-biased expression are more variably expressed between strains. These data strongly support the idea that genes with male functions evolve more rapidly than those used for other functions. Interestingly, female-biased gene expression may be much more constrained than unbiased gene expression.

Microarray analysis shows that roughly 50% of the genes in *D. melanogaster* show significant sex-biased expression in adults (Jin *et al*, 2001; Meiklejohn *et al*, 2003; Ranz *et al*, 2003), mostly due to differences in the germline (Andrews *et al*, 2000; Arbeitman *et al*, 2002; Parisi *et al*, 2003). Genes with male-biased expression turn over rapidly in terms of both gene expression over a $\sim$2.5 million year time scale (compared to *D. simulans*, Meiklejohn *et al*, 2003; Ranz *et al*, 2003) and sequence over a $\sim$250 million year time scale (compared to *Anopheles gambiae*, Parisi *et al*, 2003). Genes with unbiased or female-biased expression show greater expression and sequence conservation. Thus, at least for *Drosophila*, the rapid evolution of functions involved in reproduction applies to males, but not females. This does not necessarily contradict the previous idea of rapidly evolving genes for general reproductive functions, as many of those studies focused on male reproductive function (Singh and Kulathinal, 2000).

Variation is the fuel for selection and drift. How much variation in sex-biased gene expression is available today? Meiklejohn *et al* evaluated differential expression between males from eight strains of *D. melanogaster* to find out (Meiklejohn *et al*, 2003). They sorted genes into male-biased, unbiased, and female-biased in both *D. simulans* and *D. melanogaster*. Polymorphic expression in these sets was examined in the *D. melanogaster* strains. While the magnitude of the differences between strains is not as high as between species, pairwise combinations nevertheless show that 4–19% of the genome is polymorphic for expression, and a shocking 47% is polymorphic in at least one of the strains relative to the others. Most of this is due to variation in male-biased expression. These strains are able to interbreed, so if one reasonably assumes that male bias and male function (like fertility and mating success) are positively associated, then there is a lot of variability in the male population available for selection.

Meiklejohn *et al* also extracted pre-existing array data on isolated female and male *Drosophila* tissues from the NCBI GEO database (Edgar *et al*, 2002; Parisi *et al*, 2003) (highlighting the great value of such public repositories) to determine if the overall pattern of high expression polymorphism in males holds for all tissues (Meiklejohn *et al*, 2003). Genes were sorted into testis-biased, ovary-biased, and unbiased from testis *vs* ovary arrays and male-soma-biased, female-soma-biased and unbiased for gonadectomized flies. The majority of the expression polymorphism is attributable to the testis, while there is very little polymorphism attributable to the ovary (indeed, genes with ovary-biased expression are less variable than genes with nonsex-biased expression in the gonads). An interesting difference was seen in the nongonadal soma, where genes with either male- or female-biased expression showed more polymorphic expression than genes expressed in an unbiased fashion. A simplistic ranking for polymorphic expression is testis > male nongonadal = female nongonadal > unbiased > ovary. This represents a major refinement on the idea of the rapid evolution of reproductive functions, as both the sex and the tissue in which a gene is expressed appear to affect the rate of change.

This and other global expression studies raise many questions, two of which are addressed by Meiklejohn *et al*. The assorted patterns of polymorphic expression in the strains indicate the presence of many segregating alleles. Is the underlying nature of this expression polymorphism *cis* or *trans* regulation? Many genes expressed in both *Drosophila* testis and ovary have alternative sex-specific (or sex-biased?) promoters (Misra *et al*, 2002). It will be interesting to see if mutations in those male-specific promoters are associated with polymorphic expression, and indeed Meiklejohn *et al* predict that the majority of expression polymorphism will map to *cis* regulatory sequences in the genes with polymorphic expression. However, it is also true that males express testis-specific components of the basal transcriptional machinery (TAFs and TATA family members) (Levine and Tjian, 2003). Meiklejohn *et al* note that there is slightly more variability even in the expression of unbiased genes in males, which supports the idea that more global modifiers are at work. Also, a recent array study showing preferential misexpression of genes with male-biased expression in *D. simulans* $\times$ *D. mauritiana* hybrids (Michalak and Noor, 2003) may also suggest that an altered regulatory network is at least one component of the high expression polymorphism.

A bigger question is why there is so much polymorphism in the expression of genes in the testis at all. As pointed out by Meiklejohn *et al*, genes with testis-biased expression are probably under greater net positive selection. Alternatively, high levels of gene expression in the testis (and the soma of both females and males, and reduced polymorphism in the ovary) may have little to do with function, although this seems unlikely. Perhaps new genes, or new gene functionality, important for males arises to fill a niche left by higher turnover of male-biased genes. Experimental work to try to find associations between male fitness and male-biased gene expression polymorphism would help to answer this question.

B Oliver is at the Laboratory of Cellular and Developmental Biology, National Institute of

Diabetes, Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD 20892-8028, USA.

e-mail: oliver@helix.nih.gov

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