<Further Development 6_08>

# Brain Sex in *Drosophila*

Our discussion of sexual dimorphism in *Drosophila* has so far been limited to nonbehavioral aspects of development. However, as in mammals, there appears to be a separate “brain sex” pathway in *Drosophila* that provides individuals of each sex with the appropriate set of courtship and aggression behaviors. Among Drosophila, mating takes place soon after the flies emerge from their pupal cases and does not need to be learned. Thus, the mating behaviors seem to be “hard-wired” into the insect genome.*

The behaviors of *Drosophila* courtship and mating are quite complicated. A male must first confirm that the individual he is approaching is a female. Once this is established, he must orient his body toward the female and follow a specific series of movements that include following the female, tapping the female, playing a species-specific courtship song by vibrating his wings, licking the female, and finally, curling his abdomen so that he is in a position to mate. Each of these sex-specific courtship behaviors appear to be regulated by the products of *fruitless*, a gene expressed in certain sets of neurons involved with male sexual behaviors. These include subsets of neurons involved in taste, hearing, smell, and touch, and in total they represent about 2% of all the neurons in the adult male (Lee et al. 2000; Billeter and Goodwin 2004; Stockinger et al. 2005). Fruitless also retains certain male-specific neural circuits; the neurons in these circuits die during female development (and in *fruitless* mutants; see Kimura et al. 2005).

As with *doublesex* pre-mRNA, the Tra and Tra2 proteins splice fruitless pre-mRNA into a female-specific message; the default splicing pattern is male. So the female makes Tra protein and processes the *fruitless* pre-mRNA in one way, whereas the male, lacking Tra, processes the *fruitless* message in another way. Female *fruitless* mRNA includes a termination sequence in an early exon; therefore the female does not make functional *Fruitless* protein (Figure 5.20B). The male fly makes an mRNA that does not contain the stop codon (Heinrichs et al. 1998), and the protein it transcribes is a zinc-finger transcription factor. Using homologous recombination to force the transcription of particular splicing forms, Demir and Dickson (2005) showed that it is Fruitless, and not the flies’ anatomy, that controls their sexual behavior. When female flies were induced to make the male-specific Fruitless protein, they performed the entire male courtship ritual and tried to mate with other females.

In normal females, the courtship ritual is not as involved as in males. However, females have the ability to be receptive to a male’s entreaties or to rebuff them. The product of the *retained* gene (rtn) is critical in this female mating behavior. Both sexes express this gene, since it is also involved in axon pathfinding. However, female flies with a loss-of-function allele of *rtn* resist male courtship and are thus rendered sterile by their own behavior (Ditch et al. 2005).

The splicing of the *fruitless* transcripts not only regulates sex-specific courtship patterns, it also regulates sex-specific aggression patterns as well. Female flies having a male Fruitless protein not only tend to court females, they also will fight males and try to establish themselves at the top of a dominance hierarchy. Male flies having a mutant *fruitless* allele will show female-specific aggression against other females (Vrontou et al. 2006). It appears that the presence or absence of Fruitless proteins generate male- and female-specific neural circuits that drive these behaviors. In this manner, the same stimulus (such as a pheromone) will activate different circuits and elicit different behaviors from male and female flies (Ruta et al. 2010; Yu et al. 2010; Ito et al. 2012).

*This is not to say that flies don’t learn; indeed, one thing they do learn is to avoid bad sexual encounters. A male that has been brushed off (quite literally) by a female because she has recently mated hesitates before starting to court another female (Siegel and Hall 1979; MacBride et al. 1999).