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The fruits of fly research

The sequencing and annotation of the *Drosophila* genome has been widely applauded as a tremendous scientific and organizational achievement. It is only the second sequence of an organism with a nervous system (the first being the nematode *Caenorhabditis elegans*), and a News and Views on page 424 of this issue discusses the lessons that are emerging from what might be called 'comparative neurogenomics'. But *Drosophila* is already an important model organism in neuroscience; not only is it far more complex than *C. elegans* both anatomically and behaviorally, it is also more accessible to electrophysiology. Recent work suggests it may soon yield answers to a several major questions in molecular, cellular and even behavioral neuroscience.

The same week that the genome sequence was announced, a paper[1] described the identification in flies of what may be the long-sought receptor for mechanical stimuli. Mechanoreception—a broad category that includes hearing, touch, balance and proprioception—is, along with taste, the least well understood of the senses, and the molecule(s) that transduce mechanical stimuli remain unidentified. Now, using a combination of physiology and genetics, a group in San Diego has identified what seems to be a mechanosensitive ion channel. By recording from fly bristles, the authors could detect responses resembling those of vertebrate hair cells. By recording in mutant flies selected for their impaired behavioral responses to touch, they were able to identify a gene whose mutant phenotypes suggested it might encode the channel. The gene, which they name NOMC, appears from its sequence to encode a novel cation channel, and the long string of ankyrin repeats at the N-terminus suggests that it might be linked to the cytoskeleton, a possible anchorage site for detection of force. The expression pattern of NOMC suggests a role in both touch and proprioception. It should now be possible to search for vertebrate homologs and to determine whether they have similar functions, including perhaps a role in hearing.

Another area in which flies seem poised to make a major contribution is chemoreception. By searching through the fly genome dataset, several groups have been able to identify large gene families of G protein-coupled receptors that are likely to represent smell[2–4] and possibly taste[5] receptors. The evidence remains circumstantial, but assuming these functional interpretations are correct, it should now be possible to use genetic methods to answer a variety of questions, not only about chemotransduction mechanisms but also about the wiring of the olfactory and taste systems. The latter will have broad implications for the basis of synaptic specificity; odorant receptors (and perhaps also taste receptors) are expressed in a stereotypic pattern, and to generate appropriate behaviors, each neuron must select synaptic targets that are appropriate for its particular receptor specificity. A similar problem arises in mammals (which have even more olfactory receptors than flies), and the availability of a genetic model should now allow rapid progress.

The greatest strength of the genetic approach is its ability to uncover new molecules without making any prior assumptions. For example, a recent paper[6] describes the results of a genetic screen for mutations that affect dendritic arborization, about which almost nothing is known. By expressing the fluorescent marker GFP in neurons of the peripheral nervous system, the authors could observe how dendritic arbors develop in live embryos. They then isolated mutations that disrupted the normal pattern, and were able to identify a variety of genes, including receptors, intracellular messengers and cytoskeletal regulatory proteins, that should eventually lead to a molecular understanding of dendritic growth.

The parallels between flies and vertebrates are less clear at the behavioral level, but one area that now appears ripe for investigation is sleep. Two papers within the last few weeks[7,8] have reported that *Drosophila* show periods of inactivity and reduced alertness that, like sleep, display a circadian periodicity but are also under homeostatic control, in the sense that they can be prolonged by 'sleep deprivation'. The availability of a genetic model should lead to a better understanding of how sleep is controlled, and might even provide much-needed insights into the deeper question of why it is necessary at all.

These and many other projects should benefit greatly from the *Drosophila* genome project, but to what extent will their findings translate to the mammalian nervous system? As a model for development, the track record of *Drosophila* has been excellent—it has probably contributed more to the understanding of general principles of embryogenesis than any other organism. As Miklos and Maleszka discuss in their News and Views, it is becoming increasingly clear from large-scale sequencing projects that there is extensive conservation of both sequence and biochemical function between phyla. The nervous system is no exception, and even at the cellular and developmental level, the degree of conservation is remarkable. Flies, of course, cannot provide models for higher cognitive functions, but the available evidence suggests that the evolution of complex brains depended on the elaboration of existing themes rather than any new innovations at the molecular or cellular level. Thus, as genes are discovered that influence human behavior or that distinguish us from our close primate relatives, it is likely that interpretation of their functions will depend heavily on analogies with simpler organisms.

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