PERSPECTIVES: NEUROBIOLOGY

Chaperones Take Flight

Stephen L. Helfand

Organisms as diverse as yeast, worms, flies, mice, and humans share so many essential molecular features that research on any one of them provides valuable information on all the others. The lowly fruit fly *Drosophila melanogaster* has revealed much about the mysteries of development and provided hints about the elements directing behavior and the mechanisms of aging. Building on years of experience, a number of fly researchers are using *Drosophila* as a model to study human diseases and to design new therapeutic strategies for treating them. On page 865 of this issue, Auluck *et al.* (*1*) demonstrate the value of *Drosophila* for understanding Parkinson's disease (PD), a neurodegenerative disorder of aging, and their findings may perhaps lead to a therapy for this debilitating movement disorder.

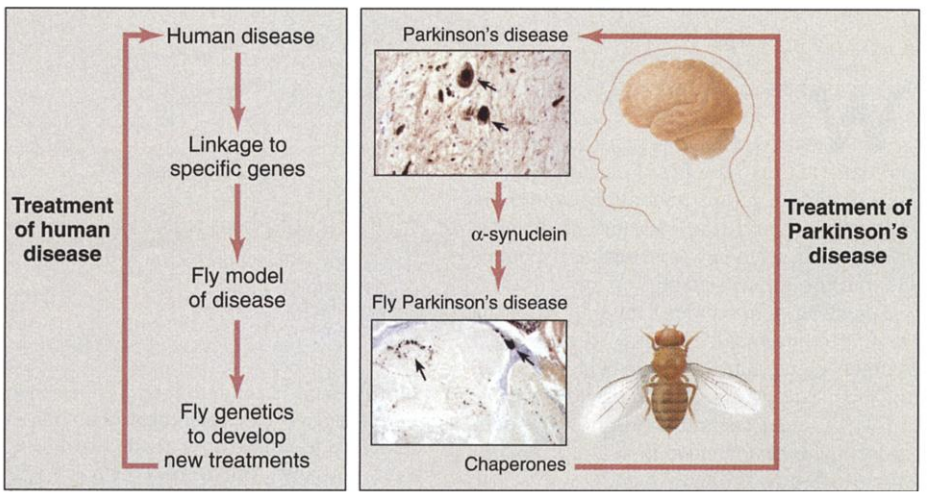
The short generation time of the fly, combined with a vast array of genetic information—including a fully sequenced genome and the availability of thousands of stocks containing mutations in many (and soon all) genes—establish *Drosophila* as an unmatched and uniquely flexible model with which to address important biomedical questions. The ability to alter the expression of any gene in any cell, at any time throughout the fly's life-span, enables experimenters to have complete control. With forward genetics (screening for random gene alterations) or reverse genetics (identifying candidate genes), researchers can dissect any biological feature of the fly, as simple as the color of its eyes or as complex as its courtship behavior. The short life-span of the adult fly, ranging from weeks to months, facilitates rapid investigation of age-dependent disorders that would take years using mammalian systems. The fly, with its large repertoire of complex behaviors and age-dependent changes, is by no means a simple animal.

Several inherited neurodegenerative diseases, including Huntington's disease and spinocerebellar ataxias 1 and 3, have been modeled by expressing the offending mutant human gene in the fly nervous system (*2*). However, there has been concern that these fly models may not faithfully mimic the human diseases because the expression of the "toxic" mutant proteins may nonspecifically disrupt the cellular machinery of neurons. The recent work of Feany and Bender firmly establishes the fly as a valuable model of neurodegeneration (*3*). When these investigators expressed the human α-synuclein gene (which is mutated in rare cases of inherited PD) in the fly nervous system, the flies displayed several characteristics of human PD. Affected flies showed a late-onset progressive degeneration of subsets of dopaminergic neurons. They also developed filamentous protein aggregates rich in α-synuclein within the cell bodies and neurites of dopaminergic neurons, which resembled the Lewy bodies and neurites characteristic of human PD pathology (see the figure).

PD is the second most common human neurodegenerative disease, affecting 1 to 3% of persons over the age of 65 and 10% of those over 80. Progressive loss of dopaminergic neurons in selected regions of the central nervous system, associated with formation of Lewy bodies and neurites (enriched for α-synuclein) in these neurons (*4*), results in severe movement abnormalities. The finding of mutations in genes encoding α-synuclein and parkin in rare inherited forms of human PD has accelerated the development of rodent and fly models of this disease (*5*, *6*). Drugs currently used to treat PD may temporarily improve the quality of life of PD patients, but they have side effects, their benefits are short-lived, and they do not prevent disease progression.

In their study, Auluck *et al.* propose a new approach to treating PD that could potentially halt and perhaps even reverse neurodegeneration (*1*). Taking their cue from work on other human neurodegenerative disorders modeled in the fly and mouse (*2*), Auluck and colleagues hypothesized that PD, a disorder involving protein misfolding and aggregation, could perhaps be treated by boosting the amount of chaperones in neurons. Chaperones are heat shock proteins, up-regulated during the stress response, that help misfolded proteins to refold (*1*). The authors report that expression of the gene encoding the human chaperone Hsp70 in the nervous system of PD flies completely prevents late-onset loss of dopaminergic neurons induced by expression of human α-synuclein. In contrast, decreasing endogenous chaperone activity accelerates the course and severity of neuronal loss in PD flies. These data show a direct relationship between the PD-like illness exhibited by PD flies and the amount of chaperone proteins in dopaminergic neurons. A link to human PD is suggested by the authors' identification through immunostaining of the Hsp70 and Hsp40 chaperones within Lewy bodies and neurites in human PD brains.

How might chaperones protect neurons? The investigators rule out the possibility that an increase in intracellular chaperones prevents the formation of protein aggregates by showing that the number,



The destiny of a fly. The link between α-synuclein and PD in humans and flies. The two characteristic pathologies of PD are the selective degeneration of subsets of dopaminergic neurons and the deposition of protein aggregates enriched for α-synuclein in Lewy bodies (insets, black arrows) and Lewy neurites (*3*). An increase in the amount of chaperone proteins in dopaminergic neurons slows the progression of fly PD, suggesting a possible therapeutic intervention for treating the human disease (*1*).

PHOTO INSERTS: P. AULUCK AND N. M. BONINI

The author is in the Department of Genetics and Developmental Biology, University of Connecticut Health Center, Farmington, CT 06030, USA. E-mail: shelfand@neuron.uchc.edu

morphology, and distribution of Lewy bodies and neurites in the dopaminergic neurons of PD fly brains does not change even after coexpression of Hsp70 and subsequent neuronal rescue. It is possible that chaperones "detoxify" the protein aggregates in a more subtle way. Alternatively, intracellular aggregates or misfolded α-synuclein may sequester chaperones, depleting intracellular chaperone stores and leaving neurons vulnerable to common environmental stresses. The ability of chaperones to prevent neurodegeneration may explain the diversity of insults associated with an increased risk of this disease, as well as the puzzling protective effect of smoking (*4*). Risk factors may hamper the normal activity of chaperones, thus accelerating neurodegeneration, whereas the oxidative damage caused by smoking may induce a general stress response that increases production of chaperones and inadvertently protects neurons.

Chaperone therapies are already in clinical trials for treating tumors and could be quickly tested for their therapeutic potential in PD. In the brief time elapsed since the first report of α-synuclein mutations in PD patients (*7, 8*), a fly model for PD has been created that can be used for screening potential therapeutics. The work of Auluck and co-workers has revealed one innovative way in which the demise of dopaminergic neurons in PD patients can be arrested and perhaps even reversed.

References

1. P. K. Auluck, H. Y. E. Chan, J. Q. Trojanowski, V. M.-L. Lee, N. M. Bonini, *Science* **295**, 865 (2002).
2. M. E. Fortini, N. M. Bonini, *Trends Genet.* **16**, 161 (2000).
3. M. B. Feany, W. W. Bender, *Nature* **404**, 394 (2000).
4. A. E. Lang, A. M. Lozano, *N. Engl. J. Med.* **339**, 1044 (1998).
5. M. F. Beal, *Nature Rev. Neurosci.* **2**, 325 (2001).
6. M. Goedert, *Nature Rev. Neurosci.* **2**, 492 (2001).
7. M. H. Polymeropoulos *et al.*, *Science* **276**, 2045 (1997).
8. R. Kruger *et al.*, *Nature Genet.* **18**, 106 (1998).

PERSPECTIVES: APPLIED PHYSICS

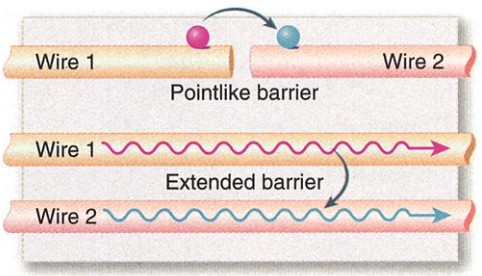
Ultrasmall Wires Get Excited

Ulrich Zülicke

When spectroscopy was invented one-and-a-half centuries ago, it yielded a bonanza of experimental data that revolutionized our understanding of the structure of matter, eventually triggering the birth of quantum mechanics. Since then, ever new and refined spectroscopic tools have enabled quantitative investigation of specimens ranging from the cosmological scale down to the smallest known elementary particle. On page 825 of this issue, Auslaender *et al.* advance the most modern variant of tunneling spectroscopy to have a close look at the dynamics of electrons in ultrasmall wires (*1*). Their results reveal the importance of interactions in low dimensions and allow a glimpse at one of its more exotic consequences: the fractionalization of electrons.

To achieve this goal, Auslaender *et al.* have built an electronic device that allows them to measure the current through a thin but highly insulating barrier between two parallel quantum wires. Defeating the laws of classical physics, electrons as quantum particles are able to tunnel through such an insulating barrier. This is possible because quantum-mechanical wave functions of electrons in the two quantum wires, which are quasi–one-dimensional electronic waveguides, overlap in the barrier. As a result, a finite probability exists for transfer of an electron from one wire through the barrier into the other one.

However, a tunneling process generally costs energy because removal of an electron from one wire and its subsequent addition to the other one excites the double-wire system. The excitation energy must be supplied by an external voltage bias, V. Energy conservation restricts possible tunneling processes to those that leave the double-wire system in an excited state with energy exactly equal to eV, where $-e$ is the electron's charge. The change in tunneling current that results from a small increase in voltage is therefore a direct measure of the number of excitations at this energy. The widespread use of tunneling as a spectroscopic tool is based on this fact (*2*).



Pointlike and extended barriers. The power of Auslaender *et al.*'s experimental setup lies in the ability to create an extended barrier between two wires **(bottom)**. Previous studies could only create pointlike barriers **(top)**.

In previous experiments (*3–5*), tunneling of electrons between quantum wires occurred through pointlike barriers. The feat achieved by Auslaender *et al.* is the fabrication of an extremely uniform extended tunnel barrier between the two parallel wires (see the first figure). In quantum mechanics, every symmetry results in conservation of an associated observable. In the present case, translational invariance along the uniform barrier makes it impossible for electrons to change their momentum in a tunneling event. The requirement of simultaneous conservation of energy and momentum severely restricts the number of possible tunneling processes.

The tunneling constraints in the two-wire device can be illustrated by a simple diagram (see the second figure). The energy of free electrons in a quantum wire depends quadratically on their one-dimensional momentum p, with mass m entering in the proportionality factor: $E(p) = E_0 + p^2/(2m)$. The energy offset E_0 arises from size quantization when fabricating a quantum wire. Energy and momentum of a tunneling electron can be simultaneously conserved at the points where the two parabolas intersect. There is no such point in the left panel of the second figure and, hence, no tunneling current in that situation. A tunneling current can, however, be induced by tuning the voltage and/or an external magnetic field. The spectroscopic power of the experimental setup implemented by Auslaender *et al.* arises from this tunability.

We can account for a voltage bias V in our diagram by introducing a relative shift of the two parabolas in the vertical energy direction by eV. At a certain voltage, the two parabolas overlap and, suddenly, electrons can tunnel while conserving energy and momentum (second figure, middle panel). Monitoring the tunneling current while changing the voltage, Auslaender *et al.* observe a resonance at a particular voltage that corresponds to the difference ΔE_0 between the two wires. No such information would emerge from point-contact tunneling spectroscopy, where the current rises linearly with voltage over a wide range of bias voltages, telling us only that electrons tunnel between two metallic wires.

The effect of a magnetic field B applied perpendicularly to the plane of the two wires is complementary to that of voltage. It can be modeled in our diagram as a relative shift of parabolic dispersion curves in

The author is at the Institut für Theoretische Festkörperphysik, Universität Karlsruhe, 76128 Karlsruhe, Germany. E-mail: ulrich.zuelicke@phys.uni-karlsruhe.de