to one another specifically through their amino-terminal extracellular domains protruding from the cell membranes. This binding would mediate cell-cell adhesion (*12*, *13*) and transmit a signal into the neuron that ultimately causes certain normal responses. This normal signaling function, however, would not directly result in Aβ production. Instead, as a by-product of the intercellular interaction of βAPP and S182 (or STM2), perhaps by the process of mutual capping (*13*) of the two proteins into the membrane regions of cell-cell contact, vesicles would be pinched off the cell surfaces and incorporated into the interior of the neuronal cell (see figure). These vesicles would then fuse with multivesicular bodies inside the neuronal cell, where the βAPP would then be proteolyzed by enzymes in the multivesicular bodies, Aβ being a product of this proteolysis. The usual intracellular traffic between the lysosomal compartment and the plasma membrane would then release the Aβ from the neuronal cell, resulting ultimately in the formation of the extracellular neuritic plaques containing Aβ.

Previous proposals about the mechanisms of formation of Aβ in AD have suggested that it is produced by normal βAPP trafficking and turnover within neurons (*2*). Indeed, cultured cells expressing βAPP secrete Aβ in the conditioned media (*14*). However, a problem with these proposals is that βAPP turns over with a normal half-life of the order of one or a few hours (*15*), many orders of magnitude faster than neuritic plaque formation in AD. Furthermore, because βAPP is a ubiquitous cell surface protein of neurons, it is not clear how the selective deposition of the plaques in specific regions of the brain would occur. In addition, these proposals do not explain how S182 and STM2 contribute to the onset of AD.

In contrast, our proposal provides direct roles for S182 and STM2 in AD, and for βAPP as a cell-cell adhesion molecule (*12*). It can explain selective production of Aβ in the hippocampus and adjoining cortex if the specific interaction between βAPP and S182 or STM2 required a particular form of regionally expressed βAPP [perhaps βAPP 695 (*16*)], S182, or STM2. The production of Aβ as a product of the cell-cell interaction system would be distinct from Aβ production by the normal turnover of βAPP on neurons and might therefore occur at a much slower rate, consonant with the usual late onset of AD. Finally, our proposal suggests new avenues of experimentation that may lead to a better understanding of the nature of AD.

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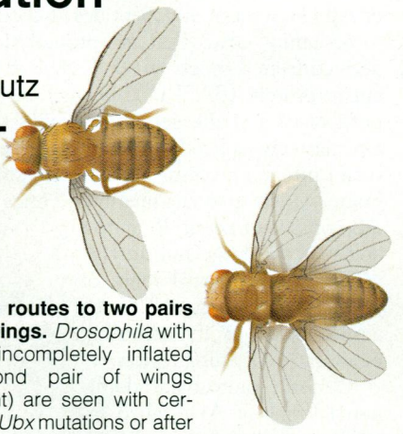
Selector Genes, Polymorphisms, and Evolution

Diethard Tautz



Two routes to two pairs of wings. *Drosophila* with an incompletely inflated second pair of wings (right) are seen with certain *Ubx* mutations or after exposing flies with a particular polymorphism in the *Ubx* gene to ether. Wild type, left.

Selector genes, master regulators of other genes, were originally proposed to define restricted areas in the developing fly called compartments (*1*). Although this idea of selector genes is now embedded in the concept of developmental hierarchies of genes, it still has a special utility when the evolution of developmental processes is considered, a point emphasized by new results on the selector gene *Ultrabithorax* (*Ubx*) from Gibson and Hogness (*2*).

Selector genes activate "realizator genes" (*1*), which eventually build the anatomical structures of the adult body. Ectopic expression of a selector gene can completely reprogram a compartment, sometimes leading to a fully developed morphological structure in the wrong place on the body (*3*). The most famous examples of this phenomenon are the *Drosophila* homeotic mutants, with legs instead of antennae or with four wings instead of two. Such mutants have sometimes been considered the perfect raw material for evolution, because single mutational events could bring about large and sudden changes and might create "hopeful monsters."

A population geneticist would instead see these animals as "hopeless monsters." Such a large morphological change is not likely to be adaptive. Although it might confer new features, it would also disrupt other adaptations and would make the individual less viable within its population. Only very strong selective advantages (which are unlikely to occur) could compensate for this. Thus, population geneticists tend to believe that changes relevant for adaptation and speciation are found in the realizator genes, not the selector genes, and that these changes generate only small steps, not large, dramatic ones. Any macroevolutionary change would have to be achieved by microevolutionary steps. Of course, over large evolutionary distances, selector genes should somehow be subject to change as well, particularly with respect to their regulatory interactions (*4*). However, a population geneticist would not normally expect to find a polymorphism with phenotypic consequences in a selector gene.

Now, Gibson and Hogness show that such a polymorphism can in fact be identified (*2*). They have analyzed a well-known phenomenon—that phenocopies of bithorax (a partial transformation of the third thoracic segment) can be produced in *Drosophila* by exposing embryos to ether vapor. Flies with a higher sensitivity to ether can be generated by repeatedly inbreeding those flies that show the strongest effects in a given generation (*5*), proving that genetic variation exists for ether sensitivity. The results of this breeding experiment had already suggested that the variation in the sensitivity to ether is likely to occur in selector, not realizator, genes, because the ether-induced bithorax phenocopies resemble known mutations in the selector gene *Ubx*. However, Gibson and Hogness have now shown that *Ubx* itself is polymorphic. They repeated the selection experiment and analyzed randomly chosen DNA polymorphisms in the region of the *Ubx* gene. They show that such polymorphisms

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are coselected, whereas unlinked markers are not. A large proportion of the genetic variation affecting sensitivity to ether is due to this polymorphism in *Ubx*.

Because the *Ubx* gene stretches over a large distance in the genome and includes distinct regulatory elements, it might have been possible to correlate the polymorphism with a certain subregion of the gene. Unfortunately, this was difficult because the molecular markers within the *Ubx* region already show a high linkage disequilibrium in the starting population. Thus, detailed mapping was not possible. Still, there are hints that the polymorphism resides in the downstream regulatory region of *Ubx*, which includes the genetically defined *abx* and *bx* regulatory elements. In line with this interpretation is the observation that in the flies that have been selected for higher sensitivity to ether, there is an increased loss of *Ubx* expression in patches within the imaginal discs that generate the affected segment.

The authors discuss their results in the context of the homeostasis concept, which suggests that developmental decisions must be stabilized against environmental influences to achieve morphological uniformity in an unpredictable environment. They propose that the polymorphism can exist in the population because there are other stabilizing effects that compensate for its phenotypic consequences. Accordingly, the mutation becomes only visible under the additional environmental stress caused by the ether treatment. In this interpretation, the polymorphism would be neutral or nearly neutral and should underlie drift effects. Alternatively, the polymorphism could be under balancing selection to provide the population with a broader reaction norm to environmental stress. In this interpretation, the polymorphism would be adaptive and should underlie positive selection. Indeed, similar selection experiments performed 40 years ago with a different starting population (*5*) led to a similar final phenotype, suggesting that the polymorphism is adaptive.

Either way, this polymorphism is exactly the sort of variation that could be the raw material for microevolutionary changes. It does not negatively affect the viability of a well-adapted population but can nonetheless become functionally relevant when a new adaptive constraint occurs. Most important, because it underlies homeostatic effects, its morphological consequences might be subtle in the wild-type populations, and it would thus be a perfect target for microevolutionary changes.

Are there more polymorphisms of a similar type in other genes? There are hints that this is the case. These clues come from classical selection experiments on bristle number in *Drosophila*. Bristles are sense organs of the peripheral nervous system and can easily be subjected to artificial selection for an increase or decrease in number. A few loci cause the major effects. Many of these are neurogenic regulatory genes, known for their roles in other contexts (*6*). Although these do not strictly qualify as selector genes, they nonetheless occupy similar places in the developmental hierarchy.

Thus, although one would still like to believe that realizator genes bear the largest burden for new adaptations, the regulatory genes that are currently so much in the focus of developmental biology may also be very profitable objects for population genetic and microevolutionary research.

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Lord of the Rings: GroES Structure

Mark Mayhew and F. Ulrich Hartl

The chaperonins GroEL and GroES are required for the adenosine triphosphate (ATP)–dependent folding of many newly synthesized polypeptides in *Escherichia coli* (*1*). GroEL is composed of two heptameric rings of 57-kilodalton (kD) subunits (*2*), which form a central cavity that is the site of polypeptide binding (see figure, parts A and B). GroES, the critical cofactor for GroEL in protein folding, is a heptameric ring of 10-kD subunits. Under most conditions GroES forms an asymmetric complex with GroEL by capping one end of the GroEL cylinder (figure, part C). The crystal structure of the GroES homolog chaperonin-10 (cpn10) from *Mycobacterium leprae* at 3.5 Å is presented by Mande *et al.* in this issue (*3*). The structure of GroES at 2.8 Å was recently reported by Hunt *et al.* (*4*). Together these two studies provide new insight into the fascinating mechanism by which the interaction of GroES with GroEL promotes protein folding.

The cpn10 heptamer forms a structure about 80 Å in diameter and 35 Å in height, reminiscent of the dome of the Roman Pantheon (*3*). The monomer is composed of nine ß strands in two sheets arranged in a ß barrel–like fold. In the heptamer the subunits are held together by hydrophobic interactions between the first ß strand of one subunit and the last ß strand of the adjacent subunit. A large loop region, comprising residues 17 to 35, extends between ß strands 2 and 3 at the lower rim of the molecule. Although this apparently mobile loop is undefined in the crystal structure, previous studies have demonstrated that it adopts an ordered ß hairpin structure when GroES binds to GroEL (*5*). A second loop between ß strands 4 and 5 extends from each cpn10 subunit to form the apex of the dome, defining an oculus about 10 Å wide.

An interesting distinction between the otherwise very similar structures of cpn10 and GroES is the degree of flexibility in the interface between the subunits. In cpn10 there is a close to sevenfold symmetry for almost all residues (except for those in the flexible loop) as would be expected in a stable molecule (*3*), whereas the substantial deviation from such symmetry in GroES suggests a significant functional plasticity (*4*). Both proteins show pronounced hydrophilicity of the inner surface of the dome (figure, yellow areas), which contrasts with the hydrophobic character of the polypeptide-binding surface of the GroEL cavity (*2*, *6*) (figure, blue areas). The oculus in the GroES dome is lined by a ring of negative charges (21 in cpn10 and 14 in GroES) that should produce considerable coulombic repulsion and may render this region of the structure metastable (*4*). In cpn10 the inner surface of the dome exposes 42 additional positively and negatively charged residues arranged in concentric rings (*3*).

GroES cycles between a GroEL-bound and free state dependent on ATP hydrolysis by GroEL (*7–9*). The initial binding of unfolded polypeptide in the unoccupied ring of the GroEL:GroES complex (*10*) facilitates GroES release and allows the reassociation of GroES to the polypeptide-containing ring (*7*). As proposed (*11*), this reassociation is fundamental to the GroEL reaction cycle, presumably because it displaces the unfolded polypeptide from its hydrophobic attachment sites into the cavity (*12*) (see figure). The substrate protein may then start to fold within the cavity (*7*), reaching a conformation that is committed to fold to the native state without further chaperonin interaction (*12*). ATP hydrolysis in the opposite toroid of GroEL induces

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