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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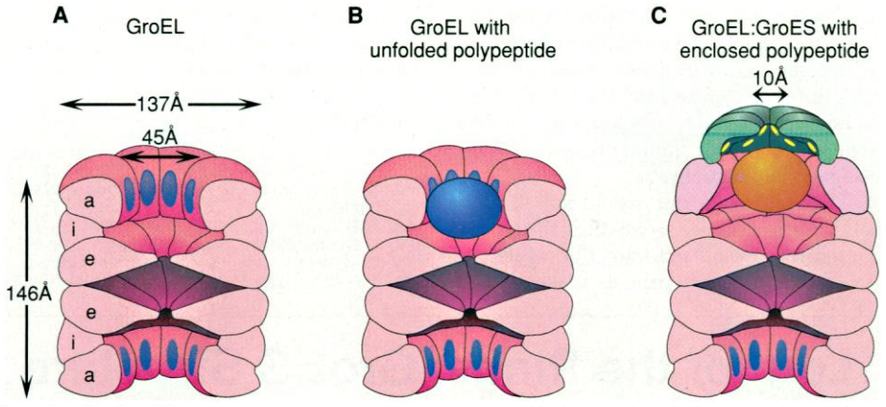

The GroEL:GroES complex helps proteins to fold. Hydrophobic binding patches (blue); charged residues (yellow); a, apical domains; i, intermediate domains; e, equatorial domains.

the dissociation of GroES from GroEL (*8*, *9*), possibly allowing release of any folded or committed substrate into the cytosol. Substrate polypeptide that has folded incompletely and still exposes hydrophobic residues will rebind to GroEL (*7*, *8*, *12*). This may result in structural rearrangement and unfolding followed by GroES rebinding.

The docking of GroES may require a recognition event on the outside surface of GroEL mediated by the mobile loop of GroES (*3*, *5*, *11*). In the cpn10 structure both lysine-36, which has been implicated in allosteric transitions (*13*), and tyrosine-73, which in GroES is close to a potential nucleotide binding region (*14*), are well positioned to interact with GroEL, possibly within the central cavity. This clamping of GroES to GroEL induces large conformational changes in GroEL, characterized by an outward movement of the apical domains (*15*) [not represented in the model of GroEL:GroES in (*3*)] (figure, part C). GroES may now interact directly with the hydrophobic polypeptide-binding regions of GroEL, which are required for complex formation with GroES (*6*). Assuming that the association with GroES masks the hydrophobic binding patches of GroEL, the net result of this conformational switching would be the release of polypeptide into a now hydrophilic cavity that is considerably enlarged and should be permissive for folding (figure, part C). Although the transfer of unfolded protein into an aqueous envrionment is sufficient to drive the compaction of the molecule, the intense hydrophilicity of the inner surface of the GroES dome may promote folding by stabilizing native-like folding intermediates (*3*). GroES may thus actually participate quite actively in the folding process.

The structural and functional studies suggest three reasons for the high efficiency of GroEL:GroES in mediating polypeptide folding: (i) the prevention of aggregation by binding unfolded or kinetically trapped folding intermediates with exposed hydrophobic surfaces; (ii) the GroES-induced release of unfolded polypeptides into a sequestered environment permissive for folding; and (iii) proofreading by rebinding and rearranging polypeptides that failed to fold sufficiently, thereby preparing them for another folding trial. A more detailed understanding of the function of GroES will come from the high-resolution structure of GroEL:GroES, which is in the pipeline.

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Approaching the Quantum Gate

The familiar desktop computer is based on a logic of ones and zeros that defines a particular set of computations. More than 10 years ago, Deutch (*1*) contributed to the creation of a new theoretical field of quantum computation, in which binary logic is replaced by fundamental computing elements that follow the laws of quantum mechanics. Just as a physical quantum system may be described by superpositions of eigenstates, a quantum computer works by processing superpositions of quantum bits or "qubits."

The field lay dormant until a theoretical discovery by Shor (*2*) that quantum computers may be capable of rapidly factoring large prime numbers, a task that is fiendishly difficult on conventional computers and so forms the basis for much present-day cryptographic data security. Unfortunately, for those desiring a quick way to crack codes, experimental realization of a quantum computer will present some extreme challenges (*3*). Nevertheless, recent work by Turchette *et al.* (*4*) and Monroe *et al.* (*5*) show that progress is being made in the laboratory.

Turchette *et al.* (*4*) have explored the possibility of implementing a quantum logic element in the form of a cavity resonator containing a single cesium atom interacting with individual photons. The cesium, prepared by optical pumping of an atomic beam, can either stay in the ground state or absorb circularly polarized light. A strong beam of light entering the cavity modifies the way a probe beam interacts with the atom. The result is an intensity-dependent phase shift between the left and right circular components of the probe beam that gives rise to conditional quantum dynamics, thus laying the foundation for photonic quantum logic circuits. Instead of a beam of atoms, Monroe *et al.* (*5*) make use of a single trapped beryllium atom to construct their prototype quantum logic gate. The result is a two-bit controlled "not" quantum gate, which, when combined with single-bit operations, is the basis for a universal logic element.

Now that quantum gates can be built, crucial issues related to the decoherence produced when quantum logic elements interact with the real world can be studied. Though a working quantum computer is far off, these experimental results are encouraging and move quantum logic from the realm of theory onto the benchtop.

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