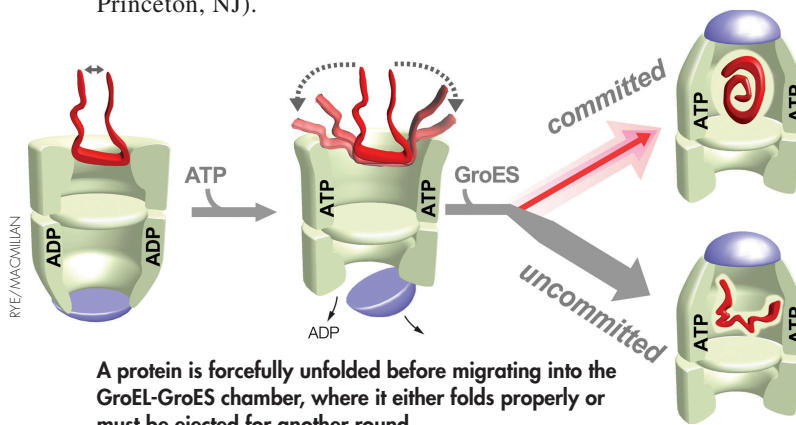


Research Roundup

To fold, first unfold

Proteins unfold at the mouth of a chaperone before being swallowed and refolded, according to Zong Lin, Damian Madan, and Hays Rye (Princeton University, Princeton, NJ).



A protein is forcefully unfolded before migrating into the GroEL-GroES chamber, where it either folds properly or must be ejected for another round.

The double-ringed GroEL chaperone complex is well-known for capturing partially folded proteins and confining them within its central cavity to facilitate folding. GroEL is especially important to proteins that have a complex folding pattern, such as Rubisco. A prominent model of GroEL function suggests that the chaperone first partially unfolds its substrate, disrupting misfolded and

inhibitory conformations, thus giving them a chance to refold properly once inside the chaperone cavity. But the importance of this effect for successful refolding has been unclear.

To explore this question, the authors tagged the two loose ends of partially folded Rubisco for FRET analysis. They found that the two ends of Rubisco were close upon initial binding to the open end of GroEL. But when ATP bound to the complex and triggered a GroEL conformational change, the Rubisco ends separated. The same conformational change allowed the complex to bind GroES, GroEL's smaller partner, thereby causing Rubisco to enter the cavity.

But did this unfolding aid in proper folding? ATP-driven unfolding works too fast to answer that question, so the authors examined the slower, passive unfolding of Rubisco on a single-ringed form of GroEL called SR1. By incubating Rubisco with SR1 for varying lengths of time before adding ATP and GroES, they showed that more time with SR1, and therefore more time to unfold before entering the SR1 cavity, produced a higher proportion of successfully folded Rubisco molecules.

"We think this represents a really clean demonstration that unfolding can directly stimulate productive folding," Rye says. **JCB**

Lin, Z., et al. 2008. *Nat. Struct. Mol. Biol.*
doi:10.1038/nsmb.1394.

GABA fine-tunes the glycine receptor

A pair of neurotransmitters deliver a one-two punch to the glycine receptor to fine-tune hearing, say Tao Lu, Laurence Trussell (Oregon Health and Science University, Portland, OR), and Maria Rubio (University of Connecticut, Storrs, CT).

"In the past, regulation of synaptic responses was assumed to be largely due to postsynaptic variables, and the transmitter was a constant," Lu says. "We are saying that the transmitters may also vary significantly in composition."

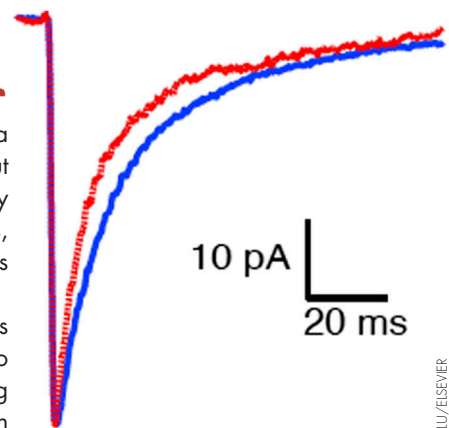
A major inhibitory neurotransmitter of the auditory pathway is glycine. The binding of glycine to its receptors briefly prevents a synapse from being activated. This inhibitory effect is thought to help the brain interpret the relative timing and intensity of signals from either ear.

Another inhibitory transmitter, called GABA, is expressed in many of the same glycine-sensitive synapses and is packaged together and coreleased with glycine in

several areas of the brain. GABA is a weak agonist of the glycine receptor, but it is too weak to activate the receptor by itself. GABA also has its own receptors, so the significance of the corelease has been controversial.

To address this question, the authors applied glycine with and without GABA to isolated membrane patches containing only glycine receptors. Glycine's inhibition of postsynaptic neuronal signaling was shortened in the presence of physiological levels of GABA. More GABA caused an even faster loss of inhibitory power.

In vivo, the two transmitters occurred together in over half the presynaptic terminals in the examined auditory region. When the authors blocked synaptic uptake of GABA precursors, the acceleration effect diminished. When they mimicked the action of the glycine receptor by applying blocking currents to an auditory neuron, they found that a small change in the decay rate of the inhibitory signal had a



The inhibition of synaptic firing by glycine (blue line) is shortened by the addition of GABA (red line).

large effect on the neuron: a 1-ms reduction in the decay constant cut the neuron's inhibition window from 4 to 2 ms.

Questions remaining include how the ratio of the two transmitters is regulated and whether that ratio varies among synapses and over time. "We expect to see a wide variation in relative concentrations of the two," Trussell says, matched to the individual needs of the synapse. **JCB**

Lu, T., et al. 2008. *Neuron*. 57:524-535.