Focus on cooperativity

In biochemistry, cooperativity is a common term describing the concerted binding of ligands to a protein, or the simultaneous switching of protein conformation, but the breadth of systems that can be described by the term is growing as our detailed mechanistic knowledge of biological systems increases. In an overview of the topic, Whitty argues that cooperativity serves as the most basic type of emergent property and discusses current and future research areas that employ this mechanism [**Commentary, p. 435**]. Goodey and Benkovic trace the history of cooperativity from its early beginnings in monitoring the coordinated action of synthetic and biological molecules to the present, highlighting recent advances in our understanding of how proteins 'talk' to themselves and each other [**Reviews, p. 474**].

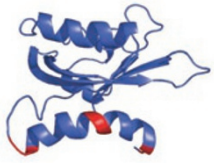
Although the folding of a single protein is well known as an example of cooperativity, recent work on RNA folding demonstrates that the phenomenon also plays an important role in these biomolecules [**News & Views, p. 451**]. Extending beyond single proteins, Williamson argues that consideration of cooperativity, in thermodynamic terms, is what's missing from our understanding of the assembly of multiprotein machines [**Perspective, p. 458**]. New technical advances will provide a strong starting point for this increased understanding, and van Oijen posits that single-molecule techniques, in contrast to the name, are well poised to quantitate cooperative interactions between interacting parts [**Commentary, p. 440**]. Multivalent binding represents another form of cooperativity; a new structure of a mannose-cleaving enzyme illustrates the coordinated interface between a protein and its polyvalent saccharide substrate [**Research Highlights, p. 457**].

Cellular communication also offers an opportunity for cooperative function. Schmidt discusses ways in which symbiotic organisms exchange molecules for mutual benefit [**Reviews, p. 466**]. Additionally, one recent paper highlights a new class of molecules that facilitate quorum-sensing but are derived from a plant compound [**News & Views, p. 452**], while another recent study demonstrates how a different quorum-sensing compound interferes with a protective host response [**Research Highlights, p. 457**]. Finally, in its broadest definition, cooperativity can include beneficial interpersonal interactions. The 4th Korea-Japan Chemical Biology symposium, a joint venture of scientists from the two countries, highlights one manifestation of people working together to achieve larger aims [**Meeting Report, p. 444**]; similarly, Scientists Without Borders, a networking database, represents a new mechanism to foster global scientific collaboration [**Elements, p. 447**]. We hope this collection of articles serves to feature ongoing research and emerging ideas and to initiate conversation as to where cooperativity exists. *CG*

The free energy of LOV

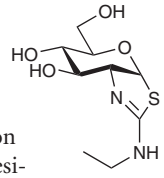
Phototropins are plant proteins that sense blue light using a noncovalently bound flavin mononucleotide (FMN) in a light, oxygen and voltage (LOV) domain. Absorption of a photon of light induces covalent adduct formation between FMN and a LOV domain cysteine, which causes the dissociation of an α-helix from the LOV domain and subsequently leads to the activation of a C-terminal Ser/Thr kinase domain. Although the structural changes of this light-activated process are well characterized, the energetics of the LOV domain photoswitch have not been investigated. Yao, Rosen and Gardner used NMR spectroscopy to quantify the equilibria between the associated and dissociated helix in the dark and lit states. From this information, the authors determined that light triggers an approximately 3.8 kcal mol^{-1} shift in the equilibrium conformation of the helical peptide, which suggests that only a small fraction of the initial photon energy is used to induce protein conformational changes. [**Articles, p. 491; News & Views, p. 449**] *JK*

Chemical genetics times three



Forward chemical genetics is useful for characterizing biological systems and identifying therapeutic leads. Many approaches for performing chemical genetic screens have been developed, but they are often used independently of one another. Hoon *et al.* have now integrated three separate cell-based assays in a platform that simultaneously evaluates the effects of increasing and decreasing gene dosage on cell sensitivity to small molecules, thus improving characterization of small-molecule bioactivity. They validated the approach using eight well-studied reference compounds and then used it to examine 188 previously uncharacterized synthetic compounds, for which they were able to identify potential protein targets. They also used the platform to show that two protein phosphatase inhibitors with similar *in vitro* activities have different effects *in vivo*, and they found that combining these inhibitors can target cells with specific genotypes within a heterogeneous population. [**Articles, p. 498**] *KS*

The look of tau



The microtubule-associated protein tau is hyperphosphorylated in the brains of individuals with Alzheimer's disease. Previous studies suggest that tau phosphorylation may exist in dynamic equilibrium with tau O-GlcNAcylation—the addition of β-*N*-acetylglucosamine to serine and threonine residues. Thus inhibition of O-GlcNAcase, the enzyme that removes *O*-GlcNAc from proteins, should raise tau *O*-GlcNAc and lower tau phosphorylation levels. However, this hypothesis has not been tested *in vivo* owing to the lack of O-GlcNAcase inhibitors that can pass the blood brain barrier. On the basis of previous mechanistic studies of O-GlcNAcase, Yuzwa *et al.* have now rationally designed a potent, selective inhibitor called thiamet-G that can cross the blood brain barrier. X-ray crystal structures confirmed that thiamet-G inhibits O-GlcNAcase by binding the enzyme's active site. The authors further showed that thiamet-G elevates *O*-GlcNAc and lowers phosphorylation of tau in cultured neurons and *in vivo*, which supports the idea of a reciprocal relationship between O-GlcNAcylation and phosphorylation and indicates that the compound will be useful for further investigating the role of *O*-GlcNAc in the brain. [**Articles, p. 483; News & Views, p. 448**] *KS*

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