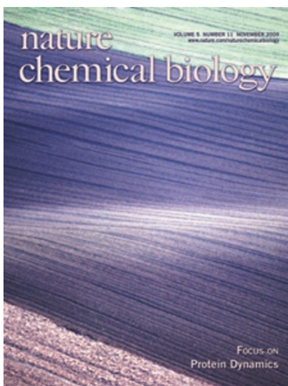


## Focus on protein dynamics

At an elementary level, much can be learned about a protein's function from gazing at its sequence and determining its higher order structure. Beyond this, understanding their role in larger complexes and enzymatic reactions is critical to fully appreciate the machinery that is built from individual proteins. For example, proteins of the eukaryotic 26S proteasome, which is responsible for regulated degradation of a variety of proteins, must assemble into a complex that is sufficiently specific and discriminatory to avoid unwanted protein destruction. Proteins destined for degradation must contain several ubiquitin-modified residues as well as an unstructured region that acts as a degradation initiation site [**Review, p. 815**]. Such unstructured or "intrinsically disordered" and highly flexible protein (IDP) regions are common in eukaryotic proteins of diverse functions and call into question whether structure is inherently important for function. Tsvetkov *et al.* propose that IDPs have protective "nannies" that allow for proper maturation and formation of functional IDP-containing complexes [**Commentary, p. 778**]. Bound to a nanny, an IDP may obtain some level of folded functional structure that evokes the induced best-fit model for molecular recognition. As an alternative to this classic view, "conformational selection" predicts that ligands select the most favored conformation from a number of pre-existing conformations [**Perspective, p. 789**], some of which may be sparse and exist only transiently, and so are "invisible" to all but the most sophisticated NMR measurements [**Review, p. 808**]. Conformational variability is also the basis of flexible backbone design, which has recently emerged for engineering protein-protein interfaces [**Review, p. 797**]. Borrowing from the idea that the function of a protein is determined by the relationship between structure and dynamics, various optical techniques are available to monitor protein dynamics over a range of timescales not accessible by the more 'static' strategies of structural biology [**Primer, insert**]. Gierasch and Gershenson argue that improvements in techniques ranging from computational analysis of systems biology data to optical imaging should be taken as an invitation to embrace the post-reductionist era of biochemistry [**Commentary, p. 774**]. The fact that nearly every major cellular process is carried out by assemblies of ten or more proteins points to a need to work as often as possible in *in vivo* systems, or to develop new strategies when this is not possible. Monitoring protein dynamics is complementary to monitoring protein structure and is clearly contributing to a more full understanding of protein function, as outlined in the collection of pieces in this issue. *MB*

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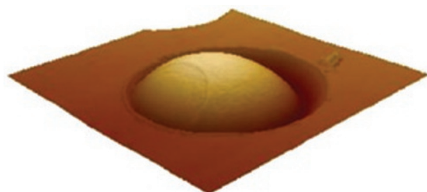
## Stress sensors get spring loaded

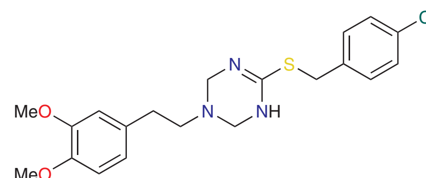


**Even with techniques like atomic force microscopy (AFM) and single-molecule force spectroscopy, studies of protein unfolding on living cells are challenging, so the strengths and mechanics of proteins in their native context are not well understood. *Saccharomyces cerevisiae* Wsc1 is a cell-surface transmembrane glycoprotein that senses the cell wall status, offering resistance to mechanical stress. Wsc1 contains a serine/threonine-rich extracellular region, glycosylation of which results in a stiff, extended rod-like structure. Dupres *et al.* used single-molecule AFM to unfold Wsc1 on live cells and found that the rod-like forms act as nanosprings when stretched and that the spring constant is reduced in response to cell wall stress. This behavior is influenced by glycan interactions, presumably to cell surface glycoproteins, since the mechanical properties are disrupted when mannosylation is blocked. Wsc1 nanospring properties explain how it can resist high mechanical forces without undergoing secondary structure unfolding.** [**Article, p. 857**] *MB*

## Flavins in tune

Part of the class of light oxygen voltage (LOV) domains are photoreceptors that are involved in processes such as phototropism and chloroplast movement. These LOV domains form a reversible cysteinyl-flavin adduct in response to blue light. Between LOV domain–containing proteins, adduct lifetimes can vary significantly, and the mechanistic basis for this variability is not understood. Zoltowski, Vaccaro and Crane created a range of site-directed mutants in Vivid (VVD), a fungal photoreceptor involved in carotenoid production and modulating circadian clock responses. Mutations in two regions of the active site altered the rate of adduct decay by over four orders of magnitude, and these rates of adduct decay correlated with receptor signaling. These results provide a detailed understanding of how the active site environment regulates adduct stability and LOV domain function and may enable the development of tunable cellular photoswitches. [**Article, p. 827**] *JK*

## Lethal via lipoproteins




Although cell-based screening offers a potential method for identifying new antibacterial compounds, identifying the targets of any leads can prove challenging. To aid in target identification, Pathania *et al.* developed an ordered array of high-expression clones of essential genes in *Escherichia coli.* Using this approach, the authors identified *lolA* as a gene that suppressed the lethality of MAC13234, a small molecule that inhibited the growth of *E. coli* in a high-throughput screen. LolA is a chaperone involved in transporting lipoproteins lacking an inner membrane retention signal to the outer membrane. MAC13234, analogously to LolA depletion, caused the most abundant *E. coli* outer membrane lipoprotein to aberrantly accumulate on the inner membrane. NMR detection of a MAC13234-LolA interaction *in vitro* provided further support that the compound directly inhibits LolA function. Bacterial lipoprotein targeting is a pathway not targeted by current antibacterials, and the activity of MAC13234 against clinical *Pseudomonas aeruginosa* isolates suggests this may be a promising new approach. [**Article, p. 849**] *JK*

*Written by Mirella Bucci & Joanne Kotz*