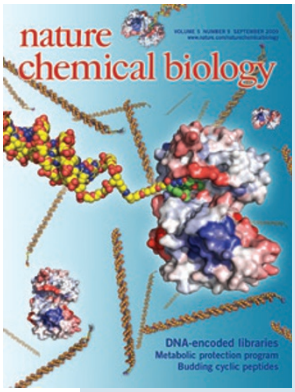


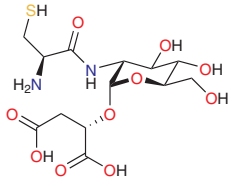
Library expansion

A number of approaches to DNA-encoded chemistry have previously been developed. However, these methods are typically limited to small library sizes. Clark *et al.* now report a new method for creating DNA-encoded libraries. Using double-stranded DNA coding and chemical and enzymatic synthesis in a split-and-pool format, the authors generated two libraries based on a triazine scaffold. Affinity selection with these libraries, the largest of which contained just over 800 million compounds, combined with high-throughput sequencing of 50,000 or more DNA tags in the selected population, led to the direct identification of potent kinase inhibitors. Combining large libraries, a modular synthetic strategy and many sequencing reads, this approach has the advantage of providing structure-activity relationships in parallel and provides an important alternative to high-throughput screening. [**Article, p. 647**] *JK*

Lysine protection program

The conversion of α-aminoadipate to lysine in *Thermus thermophilus* is closely related to bacterial arginine biosynthesis. However, while the arginine pathway relies on ArgA or ArgJ to introduce an acetyl protecting group, no homologous genes exist in the *T. thermophilus* pathway. Horie *et al.* have now discovered that LysX and LysW protect the reactive intermediates in lysine biosynthesis. The authors show that LysX catalyzes the attachment of α-aminoadipate to the C terminus of LysW via the γ-nitrogen. LysW then serves as a carrier protein in the remainder of the biosynthetic cycle, which is likely mediated by charge-charge interactions between the biosynthetic proteins. This discovery both completes our understanding of this metabolic process and highlights an unexpected strategy to control reactivity. [**Article, p. 673**] *CG*

Redox regulation



Glutathione serves a critical role in sequestering cysteine and maintaining the cellular redox state, but it is not present in all organisms. Mycothiol serves as a replacement in some species, but it is not clear how Gram-positive bacteria such as *Bacillus* spp. sequester cysteine. Newton *et al.* now use chemical sleuthing and synthesis to identify bacillithiol in *Deinococcus radiodurans* and several additional species. Biochemical studies show that the compound is substantially reduced inside the cell, at levels comparable to those of reduced glutathione in *Escherichia coli*. These results suggest that bacillithiol is the major redox-active thiol in *Bacillus* spp. and set the stage for further investigations into regulatory and synthetic processes. [Brief Communication, p. 625] *CG*

A bridge to redox state

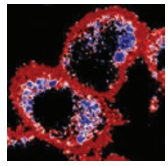
Reactive oxygen species (ROS), which are often implicated in detrimental effects on cell health, are also key players in cellular signaling and homeostasis. For instance, ROS regulate members of the FoxO transcription factor family involved in stem cell maintenance and lifespan extension. For example, FoxO4 acetylation by the acetyltransferase p300 upon ROS exposure modulates its function. Consistent with the notion that ROS signaling can be mediated by oxidation of cysteine residues and subsequent formation of intermolecular cysteine-thiol disulfide bridges, Dansen *et al.* now show that formation of a disulfide bridge between p300 and FoxO4 is required for ROS-induced acetylation of FoxO4. This defines a new mechanism for regulation of FoxO4 in processes such as cell cycle arrest and cellular metabolism. [Article, p. 664] *MB*

Written by Mirella Bucci, Catherine Goodman & Joanne Kotz

Heart help

Fibroblast growth factor (FGF) signaling through receptor tyrosine kinases invokes the MAPK signaling cascade components ERK1 and ERK2. This pathway is tightly regulated by feedback attenuators, such as the dual-specificity phosphatase Dusp6, that act directly on ERKs. Using live imaging, Molina *et al.* have screened for small molecules that modulate FGF signaling during early zebrafish development using a transgenic line that reports on FGF pathway activation. One compound, BCI, enhanced FGF signaling and was found to be an inhibitor of Dusp6. BCI appears to work by blocking substrate-induced allosteric activation of the Dusp6 catalytic site. Treatment of zebrafish embryos with BCI at various developmental stages revealed a role for Dusp6 regulation of ERK in cardiac development and highlights its potential therapeutic use. [**Article, p. 680**] *MB*

FRET on target



Förster resonance energy transfer (FRET)-based sensors have proven successful for imaging enzyme activity. In this method, a FRET donor and acceptor are attached by a cleavable linker such that enzyme activity generates a fluorescent signal. However, soluble FRET reporters cannot be used to image enzyme activity on the outside of cells. Cobos-Correa *et al.* now report the first lipid-tethered FRET probe. The reporter initially localized to the outside of the plasma membrane. Upon MMP12-mediated cleavage of the linker, the FRET donor was internalized into the cell, resulting in a lasting signal of membrane-localized MMP12 activity. The authors analyzed endogenous MMP12 activity in activated macrophages from a mouse model of pulmonary inflammation, highlighting the potential of this approach for monitoring disease. [**Brief Communication, p. 628**] *JK*

Channel conformations

IP_3 receptors are tetrameric pore loop (P-loop) calcium channels predicted to be similar in structure to other P-loop receptors such as bacterial potassium channels. Though several functional domains have been identified in these membrane proteins, the mechanism by which ligand binding translates to an intracellular signal remains unknown. Rossi *et al.* have now synthesized a panel of agonists and partial agonists to investigate receptor activation. The authors observed that partial agonists open the channel at a slower rate than agonists, which reflects a decreased ability of the ligand binding domain to communicate with the 'suppressor domain', a region known to decrease ligand affinity. These effects could be recapitulated by targeted mutations to the suppressor domain, which allowed the authors to propose a model for overall receptor structure and function. [Article, p. 631] *CG*