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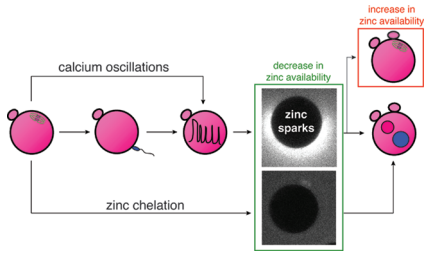
Zinc Sparks Life

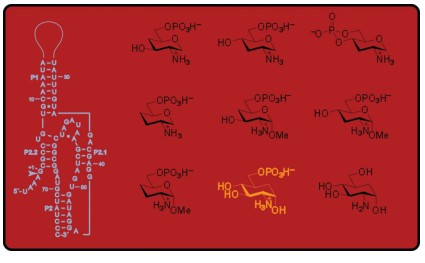
The role of cellular zinc is typically associated with its function as a cofactor or with structural maintenance in enzymes. More recent observations also point to its involvement in the regulation of the cell cycle in egg development. It is now known that the mouse oocyte absorbs billions of zinc atoms during the final stages of egg maturation prior to fertilization. In this issue, Kim *et al.* (DOI: 10.1021/cb200084y) reveal the mechanism behind the role of zinc in egg development with sparkling results.



As a mammalian egg matures, it becomes enriched with zinc. Upon fertilization, calcium levels fluctuate within the cell and influence oocyte development. Using several chemical and fluorescent probes as well as metal-modulating small molecules, the authors investigated the cellular dynamics of calcium and zinc. Calcium spikes elicited the quick release of zinc, termed zinc sparks, into the extracellular milieu within 2 h of egg fertilization. The decrease in intracellular zinc releases the egg from cell cycle arrest and initiates the earliest stages of embryonic development. This visually spectacular observation invites further research on the role of transition metals in developmental processes.

Unnatural Activation of a Riboswitch

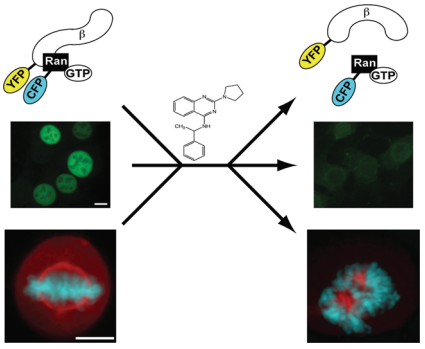
Riboswitches are RNA elements present in the 5′ untranslated region of mRNA that, upon binding cognate ligand molecules, undergo a structural change. As *cis*-acting regulatory elements, riboswitches control gene expression based on their structural conformation in approximately 4% of bacterial genes. The glmS-riboswitch regulates cell wall synthesis in Gram-positive bacteria. Lunse *et al.* (DOI: 10.1021/cb200016d) report the identification and synthesis of a potent near-cognate compound that activates the glmS-riboswitch.



The *glmS* gene encodes the enzyme, glutamine-fructose-6-phosphate amidotransferase, involved in early stages of cell wall biosynthesis. The glmS-riboswitch that regulates this gene binds and is activated by metabolite glucosamine-6-phosphate (GlcN6P). The authors in this report confirmed and characterized the presence of this riboswitch in *Staphylococci*. A small-molecule screen was performed in an attempt to identify novel activators of the riboswitch. However, this endeavor was unsuccessful. In an alternative approach, the authors rationally designed ligands that were similar to GlcN6P, which resulted in a breakthrough compound, a carba-sugar, which affected the glmS-riboswitch in a manner similar to the natural ligand. The identification of this carba-sugar provides an important advance in the development of novel therapeutic compounds targeting bacterial cell wall synthesis and growth.

New Tool for Characterizing Mitosis Regulator

The importin-β superfamily of transport receptors facilitates the import and export of cargo molecules to and from the nucleus. A GTPase enzyme, Ran, controls the directionality of this transport during interphase of the cell cycle. Additionally, importin-β and Ran are key regulators of spindle assembly during mitosis. To elucidate the precise roles of the importin-β/Ran pathway in these processes, small-molecule inhibitors of this complex are highly desirable. In this issue, Soderholm *et al.* (DOI: 10.1021/cb2000296) identify a specific cell-permeable inhibitor to the normal functioning of the importin-β/Ran complex, which opens the door for clarifying importin-β/Ran functionality.



The authors used a FRET-based high-throughput small molecule screen to identify compounds that disrupt binding between importin-β and Ran-GTP. A diaminoquinazoline compound, importazole, was found to inhibit cellular functions associated with importin-β, such as nuclear import and spindle assembly. These effects were caused *via* the direct binding of importazole to importin-β. Notably, the inhibitor was shown to be cell-permeable and revealed a novel role for the importin-β/Ran pathway in spindle positioning during mitosis. Taken together, the authors have provided a new inhibitor that will result in the improved characterization of the importin-β/Ran pathway with high temporal precision.

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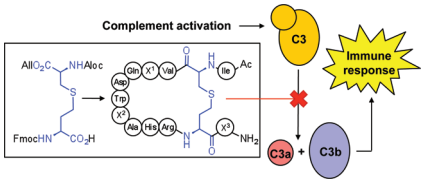
Reducing Disulfide Reduction

Disulfide bonds are key components of many bioactive peptides, providing structural stability and enhancing the binding affinity of the peptides to their target biomolecules. However, disulfide bonds are susceptible to reduction in some biological environments, which often results in a dramatic decrease in the activity of the peptide. Compstatin is a disulfide containing peptide that is a promising therapeutic for macular degeneration, a major cause of blindness in the elderly. Knerr *et al.* (DOI: 10.1021/cb2000378) now describe the efficient synthesis of compstatin analogues containing a reduction-resistant cystathionine moiety in place of the disulfide bond.



Use of a cystathionine bridge is an attractive approach for the generation of disulfide analogs because it involves the conceptually simple (though synthetically challenging) replacement of one of the sulfur atoms of the disulfide with a methylene group. The authors devise a method using solid-phase peptide synthesis and orthogonally protected cystathionine amino acid building blocks to generate numerous potent and stable compstatin analogues, an approach that can be extended to the synthesis of analogs of other disulfide-containing peptides as well.