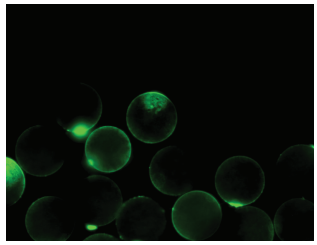
In this ISSUE

How Does the Sperm Fertilize the Egg?

The remarkable process of mammalian fertilization requires a sperm cell to successfully navigate to an egg cell, bind to receptors on its surface, and fuse with its plasma membrane. The sperm protein fertilinβ, and specifically its tripeptide sequence glutamate–cysteine–aspartate (ECD), is involved in the adhesion process, and synthetic, multivalent mimics of the ECD motif have been shown to inhibit sperm–egg adhesion. Evidence suggests that egg $\alpha_6\beta_1$ is the binding partner of fertilinβ, but conflicting reports indicate that egg integrins are not involved in fertilization. Using the synthetic ECD-containing polymers as molecular probes of the interaction, Baessler *et al.* (DOI 10.1021/cb900013d) and Point of View (DOI 10.1021/cb900110q) uncover intriguing additional evidence of the role of egg β1 integrin in fertilization.

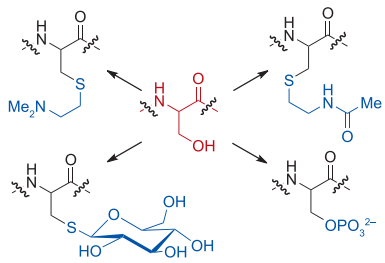
Investigation into the mechanism of inhibition by the synthetic ECD polymers revealed that the polymers do in fact directly compete with sperm binding to the egg cell surface. Interestingly, however, the function of the β1 integrin appears to be to accelerate the initial adhesion of the sperm to the membrane, while the subsequent attachment and fusion processes are likely mediated by other proteins in the integrin complex.



Natural Production of the Unnatural

Key components of cell function such as signaling pathways, cell–cell interactions, and gene regulation rely on the posttranslational modifications of proteins. Such modifications include phosphorylation, glycosylation, and methylation. Peptides containing similar modifications are valuable tools with which to investigate and manipulate these important components of protein function. Though methods for creating synthetic peptides with defined modifications have been developed, they rely on expertise in peptide synthesis and can be time-consuming and costly. You *et al.* (DOI 10.1021/cb800309v) now describe an innovative method for creating biologically produced peptides containing common posttranslational modifications found on natural proteins.

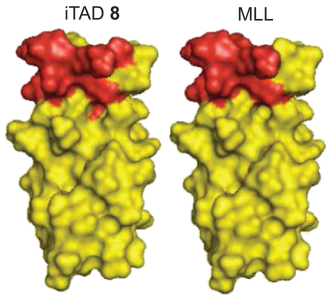
By exploiting the substrate promiscuity of lacticin 481 synthetase, an enzyme involved in the biosynthesis of antimicrobial peptides, peptides containing phosphorylated serines were produced in bacteria and purified. A wide variety of peptide sequences were tolerated, and further enzymatic and chemical treatment of the peptides enabled generation of analogs of O-linked glycopeptides and peptides with acetylated and methylated lysines.



Manipulating Transcription a TAD

Gene transcription is regulated in part by transcriptional activators, proteins composed of a DNA binding domain that controls gene targeting and a transcriptional activation domain (TAD) that controls gene activation. The importance of tightly regulated gene transcription is underscored by the alterations in transcription patterns observed in various diseases. The creation of artificial transcriptional activators that would enable external control over gene transcription is thus appealing both from a research and therapeutic standpoint. Buhrlage *et al.* (DOI 10.1021/cb900028j) now report the characterization of effective small molecule TAD mimics, referred to as iTADs.

The design of iTADs is based on natural TADS, which are amphipathic biomolecules containing strategically positioned hydrophobic and polar functional groups that engage in intricate interaction patterns with their many binding partners. iTADS employ an isoxazolidine functionality also decorated with hydrophobic and polar groups designed to facilitate similar interactions. Indeed, detailed investigation of iTAD interaction with CREB binding protein offered compelling evidence that the iTAD mimics natural TADs both functionally and mechanistically.



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