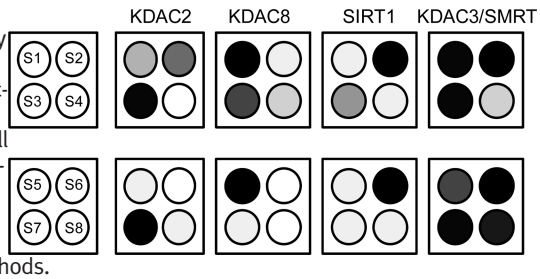
In this ISSUE

Profiling KDACs

The dynamic acetylation of lysine residues occurs throughout numerous cellular processes, but many aspects of this post-translational modification are not well understood. For example, the differential roles of the 18 distinct human lysine deacetylases (KDACs) have not been characterized, and their substrate specificities are not known. Now, Gurard-Levin *et al.* (DOI: 10.1021/cb100088g) elegantly combine the use of peptide arrays and a mass spectrometry method called SAMDI to probe the substrate specificities and specific functions of four KDACs: KDAC2, KDAC3, KDAC8, and sirtuin 1 (SIRT1).

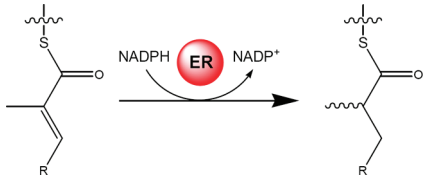
To examine KDAC substrate specificity, 361 hexapeptides in which the two residues C-terminal to the lysine residue were varied were immobilized in an array format to a self-assembled monolayer of alkanethiolates on gold. After analysis of the substrate specificity of recombinant KDACs by SAMDI, arrays of the selective substrates were used to probe KDAC activity in nuclear cell extracts and to profile KDAC activity through the cell cycle of a cancer cell line. This innovative approach offers a general route for exploring KDAC function that has distinct advantages over analogous fluorescence-based methods.



Stereochemistry by Design

Polyketides, diverse natural products with a variety of medicinal properties, are produced by bacteria, fungi, and plants. The polyketide production system in such organisms is remarkable in many ways, including its ability to precisely control the stereochemistry of specific reactions along the polyketide biosynthetic pathway. For example, while achieving a successful asymmetric hydrogenation can be exasperatingly challenging for organic chemists, the enoylreductase (ER) domain of modular type I polyketide synthases efficiently and stereospecifically reduces alkene moieties in enzyme-bound 2-enoyl thioesters. Using site-specific mutagenesis, Kwan *et al.* (DOI: 10.1021/cb100175a) now investigate which residues in the ER active site are responsible for affording such exquisite stereospecificity.

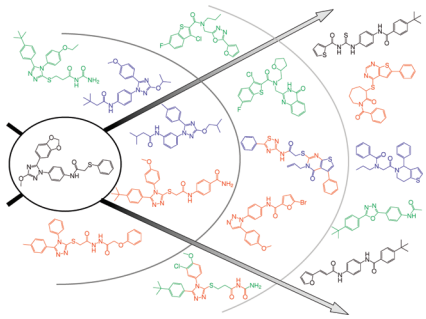
Several conserved residues in the ER active site were probed for their role in influencing the stereochemistry of the ER reaction product. Numerous residues known to be important in related enzymes were ruled out as key players, but a lysine residue was implicated as a potential proton donor for the reduction reaction. These insights could facilitate the creation of engineered ER proteins that can produce polyketides with designed stereochemical outcomes.



Making Virtual Screening of Multifunctional Proteins A Reality

Identification of novel small molecule inhibitors of valid drug targets is a key objective of the drug discovery industry, and high-throughput screening is often the method of choice for finding such compounds. However, the expense and effort involved in implementing high-throughput screens has led to the development of virtual screening methods as a powerful complementary approach for identifying lead molecules. While finding varying degrees of success depending on the target of interest and known inhibitors, virtual screening has rarely been tested in the search for inhibitors of multifunctional proteins. Now, Stumpfe *et al.* (DOI: 10.1021/cb100171c) report the development of a virtual screening approach for finding inhibitors of the cytohesins, a family of cytoplasmic proteins with multiple known functions.

Starting with the known cytohesin inhibitor SecinH3, two virtual screening approaches, fingerprint similarity searching and support vector machine modeling, were combined to find structurally diverse compounds capable of differentially inhibiting the distinct activities of the cytohesins. Indeed, specific inhibitors of guanine nucleotide exchange, insulin signaling, and leukocyte adhesion were identified from the screen.



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