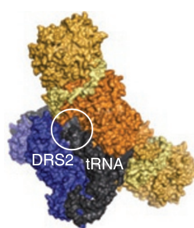
Building a bigger haystack

Combinatorial chemistry offers a powerful tool to create small-molecule libraries; however, the neccessity of screening to identify bioactive compounds limits the size and complexity of combinatorial library searches. In contrast, *in vitro* evolution strategies have permitted selection for functional nucleic acids and proteins with larger library scales and diversities. Now, Wrenn *et al.* come closer to merging combinatorial chemistry with *in vitro* evolution by combining *in vitro* selection with 'DNA translation', a previously developed approach that generates small molecules that are tethered to the DNA that encoded them. In the current work, the authors identified octamer peptidomimetic compounds called peptoids that bind the SH3 domain of c-Crk from a peptoid library generated by DNA translation. After five rounds of selection in which the encoding DNA from the immunoprecipitated peptoids was amplified and rescreened, DNA sequencing and clustering analysis identified ten classes of N-CrkSH3-binding peptoids. Independently synthesized peptoids from each class were found to bind the Crk target with affinities similar to those of ligands identified by phage display and other methods. Effective binders contained a conserved N-terminal triamine, presumed to bind SH3 as a cationic group, and also a series of small aliphatic side chains situated in the peptoid's central sequence. The selection scheme permited the rapid identification of a previously unknown class of c-Crk binders as SH3 ligands. The study demonstrates the first evolution-based approach and significantly expands the library size available for small-molecule lead discovery. (*J. Am. Chem. Soc.* **129**, 13137–13143, 2007) *TLS*

tRNAs charged and channeled

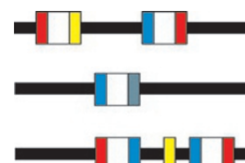


tRNAs charged with their individual amino acids are normally formed through the action of specific aminoacyl-tRNA synthetases (aaRSs) that charge the tRNAs with free amino acids. tRNAs charged with asparagine and glutamine can also be synthesized through the action of a tRNA-dependent amidotransferase (AdT) that catalyzes amidation of mischarged tRNAs, such as aspartate bound to $tRNA^{Asn}$. Because mischarged $Asp\text{-}tRNA^{Asn}$ and $Glu\text{-}tRNA^{Gln}$ are not afforded the protection that elongation factors use to protect newly charged aminoacyl-tRNAs from cleavage of their labile ester bonds, these aminoacyl-tRNA intermediates must be otherwise protected. Now, Bailly *et al.* show that this involves a direct channeling of the aminoacyl-tRNA between aaRS and the AdT. The authors used an *in vitro* system that supports aspartylation of $tRNA^{Asn}$ by DRS2, the aspartyl-tRNA synthetase, to show that AdT and DRS2 assemble with the uncharged tRNA into a ternary ribonucleoprotein complex that they named the transamidosome, a functional complex that is also formed *in vivo*. The different affinities of the various components for each other, as well as the kinetics of the aspartylation and amidation reactions *in vitro*, led them to a model in which the transamidosome uses free aspartate and an amido group donor as substrates to catalyze attachment of aspartate to the tRNA prior to its conversion into asparagine. Release of $Asn\text{-}tRNA^{Asn}$ then leads to dissociation of this dynamic complex. These steps suggest that assembly into the transamidosome enables channeling of the mischarged tRNA intermediate between DRS2 and AdT, thereby protecting the labile ester bond linking the tRNA and the amino acid from cleavage. (*Mol. Cell* **28**, 228–239, 2007) *MB*

Methylarginine returns a methyl

Methylation of histone arginine residues has an important role in epigenetic regulation. Although arginine methyltransferases are known to catalyze histone methylation, enzymes responsible for reversing the modification had not been identified. Chang *et al.* now report that the Jumonji domain-containing 6 protein (JMJD6) is an arginine histone demethylase that is part of the family of Fe(II)- and αKG-dependent oxygenases. *In vitro*, JMJD6 preferentially removed methyl groups from dimethylated Arg2 of histone 3 (H3R2me2) and Arg3 of histone 4 (H4R3me2) to produce monomethylated arginines. Consistent with this observation, *in vivo* overexpression of JMJD6 resulted in reduced global levels of H3R2me2 and H4R3me2. As predicted, the demethylation reaction required the expected cofactors and generated formaldehyde, which supports a mechanism in which the methyl group is first oxidized and then released as formaldehyde. Identifying the first arginine demethylase opens up many further questions: do protein-protein interactions target this enzyme to other methylarginine sites, or do related demethylases reverse other arginine methylations? Are misregulated epigenetic events responsible for the embryonic developmental defects observed in the JMJD6 knockout mouse? Do the cofactor requirements of JMJD6 provide a link between epigenetic modifications and cellular status? The identification of JMJD6 provides an important piece for assembling the methylation puzzle. (*Science* 318, 444–447, 2007) *JK*

The lysine code



Because of their precise patterning and the reproducibility of their formation, the complex silica skeletons of sponges and diatoms are thought to be formed by genetically driven processes. Although elucidating the details of this process has proven extremely challenging, long-chain polyamines and the proteinaceous silaffins have been shown to promote silica formation. Several species-specific polyamines have been identified, and it is anticipated that this heterogeneity, along with potentially similar variability in silaffins, is directly related to the different silica architectures observed in nature. However, investigating silaffins has been complicated because these proteins are heavily post-translationally modified, primarily via phosphorylation, methylation and amidation. In particular, silaffin-3 has 33 lysines, most of which are involved in defined K(A/S/Q)XK tetrapeptide repeats. Using mass spectrometry techniques, Sumper *et al.* have now analyzed these lysines to determine the modifications at each site, and surprisingly they found that the introduction of methyl and aminopropyl groups conforms to a specific code according to the placement of each residue within a tetrapeptide block and the relative location of these repeat units, which suggests the existence of enzymatic modification machinery that relies on primary sequence information. It remains to be seen whether the few exceptions to these rules are also enzymatically encoded, and how these patterns translate into function. In the meantime, these results outline new functional criteria that will help to define this unusual biochemical process. (*Angew. Chem. Int. Ed.*, published online 26 September 2007, doi:10.1002/anie.200702413) *CG*

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