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Structural Analyses Reveal Key Insights into Clinically Relevant Nanomachines

Humans are living longer lives than ever before, thanks in part to the development of effective drugs to treat infection and disease. For example, antibiotic daptomycin can treat complicated bacterial skin and blood infections, cyclosporin can help prevent someone from rejecting a vital organ transplant, and caspofungin can be given intravenously to treat patients with a serious fungal infection. What do these three very different drugs have in common? They are each produced by enzymes referred to as nonribosomal peptide synthetases (NRPS), nanomachines that construct a variety of molecules with significant clinical relevance as they produce a plethora of different drugs. Recent research at the APS has significantly furthered our understanding of how these nanomachines synthesize molecules. The researchers from McGill University and Yale University revealed the structural basis of this synthesizing process and these novel findings create the exciting possibility of designing new, effective drugs to improve human health.

NRPSs, which are made up of different sections called modules, can be likened to assembly line machines in factories that add building blocks to a growing molecular chain. The molecular product built by NRPSs is referred to as a nonribosomal peptide or depsipeptide. The term "nonribosomal" means that these molecules are built outside of ribosomes, which are more classical molecular machines that synthesize proteins. Peptides are made up of amino acid building blocks; the term "depsipeptide" describes a peptide with a unique chemical structure (i.e., one or more amide groups are replaced with an ester group). Depsipeptides contain both hydroxyl acid and amino acid residues, the former of which are often derived from α-keto acid substrates. Keto acids play important biological roles—e.g., keto acids are converted into energy in response to lengthy periods of food deprivation, sometimes known as intermittent fasting.

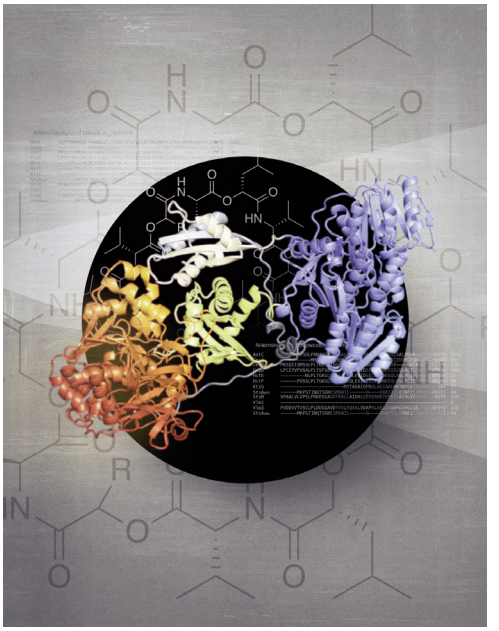

Fig. 1. Structure of a depsipeptide module, in which the PCP domain is disordered. (Photo credit: Larissa Ulisko and Martin Schmeing)

In this study, substantial structural insights have been gleaned into NRPSs. The team unveiled the architecture of NRPS modules and identified the mechanism by which α-keto acids are incorporated into the assembly process. Figure 1 displays the surprising architecture for modules that use α-keto acids. Since many nonribosomal depsipeptides derive their hydroxyl acid residue from α-keto acids, this sheds light onto a paramount part of nonribosomal depsipeptide synthesis. X-ray crystallography studies were performed at the Northeastern Collaborative Access Team beamlines 24-ID-C and 24-ID-E, and at the Canadian Light Source beamline 08ID-1 to obtain important structural data.

This research opens important possibilities for future research, as these findings advance our collective understanding of how these medically useful molecules are produced. With this knowledge, it is theoretically possible to manipulate this machinery to produce new, potent drugs capable of further improving human health. — Alicia Surrao

See: Diego A. Alonzo, Clarisse Chiche-Lapierre, Michael J. Tarry, Jimin Wang, and T. Martin Schmeing*, "Structural basis of keto acid utilization in nonribosomal depsipeptide synthesis," Nat. Chem. Biol. **16**, 493 (May 2020). DOI: 10.1038/s41589-020-0481-5

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