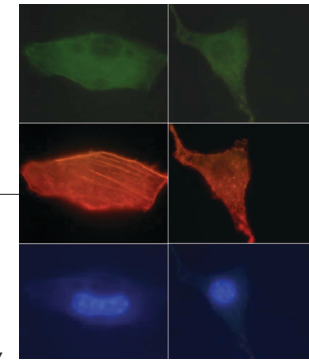
acs chemical biology

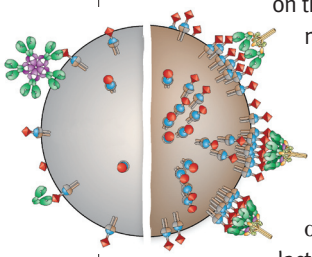
In this ISSUE



Sweet but Deadly

Multivalent binding enhances the affinity and the specificity of many biological interactions. This phenomenon is an important component of cellular recognition processes. In a therapeutic analogy to killing two birds with one stone, Carslon *et al.* (p 119) present a strategy that exploits multivalent interactions to both selectively seek out cancer cells and subsequently trigger the killing of these cells.

A bifunctional small molecule was designed to target the $\alpha_v\beta_3$ integrin, a protein overexpressed on the surface of many cancer cells, at one end and display the carbohydrate galactosyl-α(1–3)galactose (α-Gal epitope) at the other end. When the α-Gal epitope engages in multivalent interactions with anti-α-galactosyl antibodies in human serum, an immune response is triggered that results in cell lysis. When several cancer cell lines expressing varying levels of $\alpha_v\beta_3$ were exposed to the bifunctional agent, only those that expressed high levels of $\alpha_v\beta_3$ underwent cell lysis. In contrast, an $\alpha_v\beta_3$ targeting agent containing the toxic agent doxorubicin indiscriminately killed all cell lines regardless of the $\alpha_v\beta_3$ levels. The superior selectivity imparted by this strategy could lead to promising new targeting agents for cancer and other diseases.



Partnering Up

Src homology 2 (SH2) protein domains bind phosphotyrosines (pY) and thus modulate cell signaling events. Whereas the interactions between many SH2 domains and pY peptide ligands have been characterized, many of the protein partners for SH2 domains remain unknown. Wavreille *et al.* (p 109 and Point of View p 93) now present an approach for finding SH2 binding proteins.

Combinatorial chemistry and bioinformatics are blended in this strategy to identify proteins that bind to the SH2 domain of the protein tensin. Synthesis and screening of >500,000 pY-containing peptides led to the discovery of three classes of tensin-binding pY peptides, one of which was used to query databases for potential tensin binders. Two proteins identified in the database, downstream of tyrosine kinase 2 (Dok-2) and 3-phosphoinositide dependent protein kinase 1 (PDK-1), were found to interact with tensin in cells. Additionally, a cell-permeable peptide inhibitor against the tensin SH2 domain was synthesized and shown to prevent the interaction between tensin and PDK-1. This approach can be used to identify protein partners in other modular protein interacting domains.

Attack of the Pyranopyrones

Polyketides are structurally diverse compounds that possess a range of biological activities. A 4-hydroxy-2-pyrone moiety is often present in biosynthetically engineered polyketides, and its nucleophilic properties provide a unique opportunity for the creation of semisynthetic polyketide derivatives. Specifically, 2-pyrones can be synthetically transformed to pyranopyrones. Ridley *et al.* (p 104) combine polyketide biosynthesis and synthetic chemistry to prepare several novel pyranopyrones and evaluate their anticancer activity.

Four biosynthetically engineered 2-pyrone-containing polyketides were chosen as starting compounds for derivatization into pyranopyrone analogues. Reaction conditions were developed such that common polyketide functional groups like phenols and hemiacetals were well tolerated, and nine pyranopyrones were generated. The semisynthetic compounds were tested for their ability to prevent growth of three cancer cell lines relative to a known anticancer pyranopyrone. Some of the compounds had comparable activity, whereas others were less active. This mingling of biosynthetic engineering and synthetic chemistry provides unique building blocks for the creation of molecules not easily obtained by traditional methods.

The Circle of Communication

Bacteria use chemicals called autoinducers to communicate. The autoinducer AI-2 has been termed a "universal" bacterial signal because of its unique ability to be recognized by many different bacterial species. Xavier *et al.* (p 128 and Point of View p 89) characterize specific components of AI-2 signaling in enteric bacteria, revealing the mechanisms used by this species to deplete AI-2 in the intercellular environment.

The signaling system that revolves around AI-2 involves various AI-2 derivatives, processing enzymes, receptors, and gene transcription regulators, including the AI-2 precursor 4,5-dihydroxy-2,3-pentanedione (DPD), the kinase LsrK, the transcriptional repressor LsrR, and a protein of unknown function, LsrG. Thin-layer chromatography revealed that LsrK phosphorylates DPD and the phosphorylated compound, termed P-DPD, binds to LsrR, an event that leads to induction of the *lsr* operon. Further investigations with mass spectrometry and NMR studies showed that LsrG is an enzyme that converts P-DPD to 2-phosphoglycolic acid. Notably, 2-phosphoglycolic acid does not bind to LsrR and would thus result in transcriptional repression and termination of the AI-2 signaling cycle. These studies illuminate intricate details of how enteric bacteria control their environment.

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