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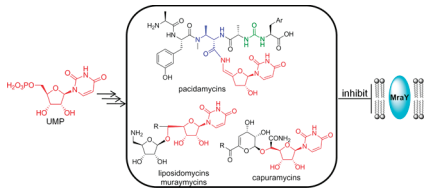
The Path to Uridyl Peptides

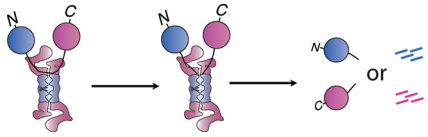
Microbes synthesize a variety of compounds with antimicrobial activity, which serve to protect the organism from other potentially threatening microbes, and are also a rich source of antibiotics for human use. Microbe-derived antibiotics come in a wide variety of flavors, containing inventive amalgamations of structural elements such as polyketides, peptides, carbohydrates, and nucleosides. Now, Walsh and Zhang (DOI: 10.1021/cb200284p) discuss the biosynthetic pathways involved in the generation of the uridyl peptide family of antibiotics.



Uridyl peptide antibiotics can be divided into numerous subclasses, including pacidamycins, mureidomycins, liposidomycins, caprazamycins, and muraymycins. These compounds target the bacterial enzyme MraY, which is involved in the biosynthesis of the bacterial cell wall and is thus a potential drug target. Recent studies have elucidated the pathways involved in generating the unusual peptide scaffolds found in these antibiotics and in the coupling of the nucleoside uridine to them. These studies have expanded our understanding of this important mechanism for antibiotic generation and provide clues toward improving this antibiotic class for potential human benefit.

Mechanism of Proteasome Degradation

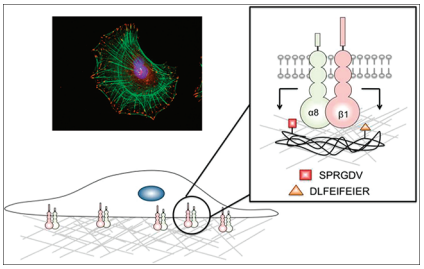
The proteasome plays a vital role in maintaining quality control of proteins in a cell. Specifically, it degrades misfolded and damaged proteins, while maintaining the appropriate concentration of important regulatory proteins. Recognition of a ubiquitin tag ensures that proteasome effects are specific and target the correct proteins. In this issue, Kraut and Matouschek (DOI: 10.1021/cb2002285) provide a clearer picture for proteasome-mediated internal cleavage of target proteins.



The authors elucidate the mechanism of protein cleavage that occurs when the proteasome binds to an internal initiation site between two folded domains. Interestingly and somewhat unexpectedly, when the proteasome binds the internal site, the stability of one domain can influence the ability of the proteasome to degrade the other adjoining domain. This seminal observation is of importance in understanding partial proteasome degradation and its effect on cell signaling.

Defining Nephronectin Binding to Clinically Relevant Receptor

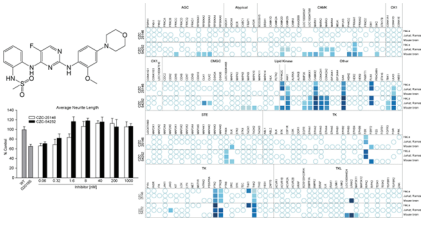
Nephronectin is an extracellular matrix (ECM) protein implicated in renal development. This protein is known to interact with the $\alpha 8\beta 1$ integrin, a receptor previously shown to be important in kidney development. Characterization of the interaction between this ECM protein and $\alpha 8\beta 1$ is important to understanding the role of this protein and integrin receptor in organ development. Sánchez-Cortés and Mrksich (DOI: 10.1021/cb200186j), through rigorous experimentation, define the key residues that facilitate binding of nephronectin to $\alpha 8\beta 1$ integrin.



Two separate motifs on nephronectin, SPRGDV and DLFEIFEIER, have been previously reported to bind $\alpha 8\beta 1$ integrin. Using a sophisticated self-assembled monolayers assay to study cell adhesion, the authors determined that these two motifs bound distinct sites on the receptor. Interestingly, these two sites have a synergistic effect on receptor binding. Additionally, peptide array experiments were used to identify FEI as the minimal sequence for binding the second motif, with the central glutamate residue being the most important binding determinant. With an improved picture of the nephronectin to $\alpha 8\beta 1$ integrin binding determinants, rationally designing ligands to modulate the activity of this receptor is now a distinct possibility.

Breakthrough in the Fight against Parkinson's Disease

Mutations in the protein kinase, leucine-rich repeat kinase-2 (LRRK2), have been associated with the development of Parkinson's disease. A potential therapeutic model for treating this neurodegenerative disease employs compounds that inhibit LRRK2. However, to date, no truly specific compound exists that targets LRRK2 without perturbing the functioning of other cellular kinases. Now Ramsden et al. (DOI: 10.1021/cb2002413) report an LRRK2-specific inhibitor that mitigates the harmful effects of LRRK2 mutants.



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The authors used a combination of quantitative chemical proteomics and targeted mass spectrometric analysis to find selective LRRK2 inhibitors. This robust approach identified CZC-25146, a compound potent and specific for reducing LRRK2-based neuronal toxicity. Apart from providing an important new lead compound in treating Parkinson's disease, this powerful chemical proteomics approach could provide for a new platform for identifying potential therapeutic agents against other major human diseases.