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Cyclic Peptides as Modulators of Protein-Protein Interactions

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Editorial

Biological processes operate through intricate networks comprised of a myriad of interacting molecules. Protein-protein interactions (PPIs) permeate these networks and are able to transmit and integrate the signalling pathways inside the cells in response to physiological and non-physiological conditions (including cellular pathologies as cancer). To assess the role of such interactions, peptidic compounds have been developed aiming to modulate intracellular PPIs. For instance, structural studies demonstrated in humans and roundworms that the α-helical MAML1 polypeptide binds to a groove formed by the PPI between ICN1 and CLS proteins. The ICN1-CLS-MAML ternary complex plays a key role on NOTCH1 signalling pathway by recruiting the transcription machinery and leading to the transcription of oncogenic NOTCH1 target genes. The group of Dr. James E. Bradner (Harvard Medical School) have designed short α-helical peptides based on a fragment of MAML1 that disrupts the PPI ICN1-CLS, repressing the transcription of NOTCH1 target genes in leukemic cells.

Cyclic peptides form a very exciting group of compounds (and yet, poorly explored) with unique properties. Compared to linear ones, cyclic peptides have higher metabolic stability and higher membrane permeability, making them suitable compounds for therapeutic applications. Cyclosporine for example, one the most medically used cyclic peptide, can easily move across cellular membranes. This compound modulates the PPI between cyclophilin and calcineurin by binding to the former and therefore inhibiting the latter. However, due to its non-canonical structure containing D- and modified amino acids, chemical synthesis of cyclosporine is expensive and laborious. To circumvent this, pharmaceutical companies extract cyclosporine as a metabolite produced by fermentation from the fungus *Beauveria nivea*, which provides a cheaper, easier and quicker method to produce it.

To fill the urgent need for compounds that modulate PPIs involved in diseases, synthetic biology is now being applied to produce, modify and test new cyclic peptides. One example comes from the group of Dr. Stephen Benkovik at Pennsylvania State University that studied the PPI modulatory role of cyclic peptides on *in vivo* assays. They have engineered a bacterial reverse two-hybrid system that evaluates which cyclic peptides from a library can inhibit a specific PPI. In this system, two interacting proteins are co-expressed as fusion proteins with bacteriophage DNA binding proteins. If the PPI is not disrupted by the cyclic peptide, the DNA binding proteins will functionally prevent expression of reporter genes and will inhibit the growth of bacteria on minimal media. However, if the PPI is inhibited by the cyclic peptide, transcription of reporter genes will no longer be repressed, and this will allow cells to grow in minimal media in the presence of Kanamycin. Dr. Benkovik group has used this powerful tool to screen a library of 3.2 million cyclic peptides. As a result, they found new compounds able to inhibit the PPI between the HIV Gag protein and human TSG101. These compounds act by partially inhibiting the viral releasing from cells, making them candidates for antiviral therapy.

The rational design of cyclic peptides, based on known peptides that naturally modulate PPIs, provides a good strategy in obtaining active compounds. Via library design and high-throughput selection, cyclic peptide scaffolds can be used to generate new variants and compounds that modulate in a precise way a broader range of PPIs. A key step in this process is the development of Synthetic Biology tools that systematically produce such cyclic peptides, introduce modifications into its scaffold, and evaluate their effectiveness over PPIs (*in vivo*). These tools will allow the discovery and the high-throughput exploitation of new compounds with important biological activity.

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