Unnatural Amino Acid Incorporation to Rewrite the Genetic Code and RNA-peptide Interactions

Thesis by

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Abstract

My general research direction is the interface between organic chemistry and biology. Interesting biological systems inspire target-oriented organic synthesis, new methodology development, and molecular design of novel materials. On the other hand, chemical synthesis prepares important biologically active compounds to be used in understanding involved mechanism and engineering biological systems.

We designed and synthesized a series of peptide-acridine conjugates based on the modular design principle to target RNA structures. Some of the peptide-acridine conjugates have substantially improved RNA-binding affinity and specificity relative to the peptide alone. We also generated various high-affinity inhibitors of the tRNA synthetases—aminoacyl sulfamide to create synthetic blanks in our translation extracts. The gaps were filled with chemically aminoacylated orthogonal tRNAs. This unnatural strategy enables peptides and proteins to be constructed containing a single novel residue at specific locations and will facilitate the mRNA display-based protein selection. To test the versatility of ribosome, we have constructed a series of puromycin analogs with natural and unnatural amino acids side chains and tested the effects of side chain characteristics of amino acid moiety on the activity of puromycin analogs. We found that amino acids of different stereo characteristics can be incorporated via puromycin route, and larger hydrophobic amino acids render higher potency.

Overall, these efforts demonstrate the successful use of a combination of molecular design as an efficient and facile method for generating new solutions to biological problems.

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