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Mini-review

Unleashing chemical power from protein sequence space toward genetically encoded “click” chemistry

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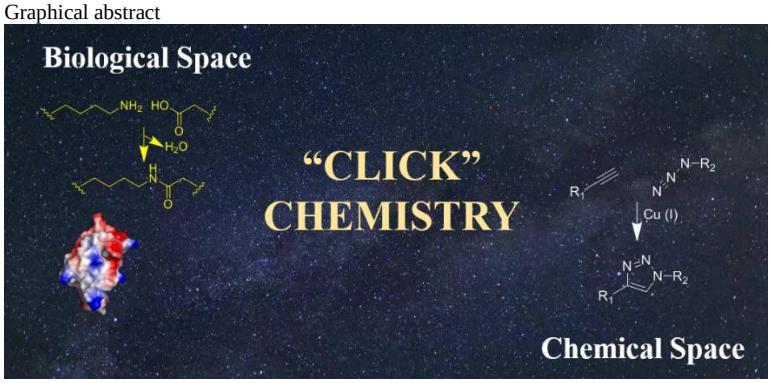
Graphical abstract



We propose the concept of genetically encoded “click” chemistry (GECC) to describe the “perfect” peptide-protein reactive partners and use SpyTag/SpyCatcher chemistry as a prototypeto illustrate their structuralplasticity, robust interaction, and versatile applications.

ABSTRACT
Synthesis of macromolecular systems with precise structural and functional control constitutes a fundamental challenge for materials science and engineering. Development of the ability to construct complex bio-macromolecular architectures provides a solution to this challenge. The past few years have witnessed the emergence of a new category of peptide-protein chemistry which can covalently stitch together protein/peptide molecules with high specificity under mild physiological conditions. It has thus inspired the concept of genetically encoded click chemistry (GECC). As a prototype of GECC, SpyTag/SpyCatcher chemistry has enabled the precise synthesis ofmacromolecules both *in vitro* and *in vivo*, exerting precise control over the fundamental properties of these macromolecules including length, sequence, stereochemistry and topology and leading to the creation of diverse biomaterials for a variety of applications. We thus anticipate a potential toolbox of GECC comprising multiple mutually orthogonal, covalent-bond forming peptide-protein reactive pairs with diverse features, which shall bridge synthetic biology and materials science and open up enormous opportunities for biomaterialsin the future.

Keywords:
Genetically encoded click chemistry
SpyTag
SpyCatcher
Topology
Protein engineering

1. Introduction

“Click” chemistry, along with its fundamental principles, has reshaped many research fields from materials science to biology ever since its conceptualization by Sharpless and colleagues in 2001 [1]. The “click” philosophy embraces a set of nearly “ideal” chemical