A RaPID way to discover bioactive pseudo-natural peptides

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The genetic code is the law of translation, where genetic information encoded in RNA is translated to amino acid sequence. The code consists of tri-nucleotides, so-called codons, assigning to particular amino acids. In cells or in ordinary cell-free translation systems originating from prokaryotes, the usage of amino acids is generally restricted to 20 proteinogenic (standard) kinds, and thus the expressed peptides are composed of only such building blocks. To overcome this limitation, we recently devised a new means to reprogram the genetic code, which allows us to express non-standard peptides containing multiple non-proteinogenic amino acids in vitro. This lecture will describe the development in the genetic code reprogramming technology that enables us to express natural product-inspired non-standard peptides and pseudo-natural products. The technology involves (1) efficient macrocyclization of peptides, (2) incorporation of non-standard amino acids, such as N-methyl amino acids, and (3) reliable synthesis of libraries with the complexity of more than a trillion members. When the technology is coupled with an in vitro display system, referred to as RaPID (Random non-standard Peptide Integrated Discovery) system as a novel "molecular technology", the libraries of natural product-inspired macrocycles with a variety ring sizes and building blocks can be screened (selected) against various drug targets inexpensively, less laboriously, and very rapidly. This lecture will discuss the most recent development of their technology and therapeutic applications toward drug discovery innovation.

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