Ribosomal synthesis of helical peptide libraries containing cyclic β-amino acids and its application to drug screening

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Peptides are an attractive drug development platform for their low manufacturing cost and little side effect. However, peptides consisting of only canonical L-α-amino acids often suffer from low target binding affinity, cell permeability, and rapid proteolytic degradation due to their flexible backbone structures. In contrast, introduction of sterically constrained nonproteinogenic amino acids, such as cyclic β-amino acids (cβaas), induces highly restricted structures of peptides, and thereby improved binding affinity against target molecules, cell permeability, and protease resistance, making them more attractive drug candidates.[1] For instance, peptides bearing periodical 2-amino-cyclopentane carboxylic acid (2-ACPC) exhibit a well-defined helical structure called 10/11/11 helix (Fig. 1a). Recently, we succeeded in ribosomal incorporation of diverse cβaas by utilizing a reconstituted *E. coli* translation system.[2] By means of this technology, we constructed a 10/11/11-helical peptide library containing 2-ACPC at every third position and applied it to an mRNA display-based screening methodology referred to as the Random non-standard Peptide Integrated Discovery (RaPID) system (Fig. 1b). The affinity screening was performed against Nrf2, which is related to the proliferation of cancer cells. As a result, we were able to obtain potent peptides with high binding affinity to Nrf2 as well as enhanced proteolytic stability compared to their α-Ala mutant counterparts. Circular Dichroism spectrometry measurement revealed that all of the discovered peptides were folded into 10/11/11 helices, showing that our strategy is practically applicable to developing a novel class of peptide drugs bearing 10/11/11-helical structures.

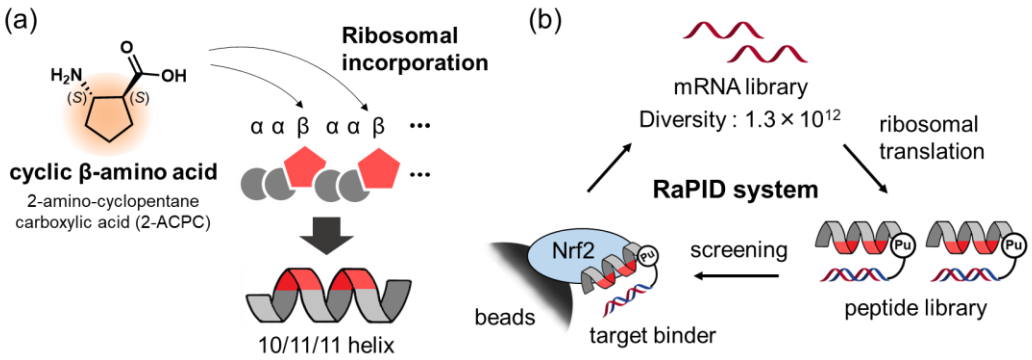

Figure 1 (a) Structure of a cyclic β-amino acid and ribosomal synthesis of 10/11/11-helical peptides. (b) The scheme of the RaPID system using a 10/11/11-helical peptide library.

[1] Gellman, S. H. et al. *Chem. Rev.*, **2001**, *101*, 3219.
[2] Katoh, T. et al. *Nat. Chem.*, **2020**, *12*, 1081.