In vitro selection of a library of pseudo-natural prenylated peptides

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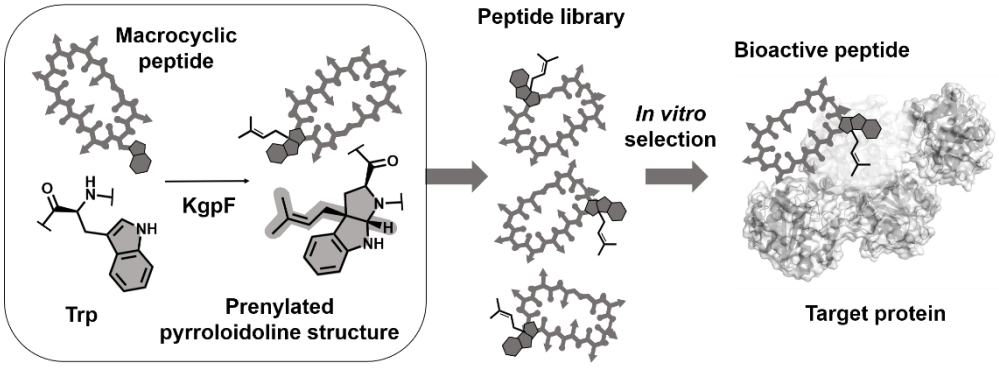
In nature, peptides undergo post-translational modification (PTM) to acquire highly complex structures distinct from 20 proteinogenic amino acids. Prenylation is a typical PTM in peptidic natural products produced by cyanobacteria, and is expected to increase membrane permeability, biostability, and rigidity of peptides. In this study, a library of pseudo-natural prenylated peptides, artificial peptides containing naturally occurring prenylated structure, was constructed. The library was applied for selection experiments to develop *de novo* bioactive peptides.

For construction of the library, an engineered *in vitro* translation system was combined with enzymatic prenylation. KgpF is a member of the prenyltransferase family involved in cyanobactin biosynthesis and utilized in this study. KgpF mediates stereospecific transfer of a dimethylallyl group to a tryptophan (Trp) and backbone ring closure, giving a tricyclic hydrophobic pyrroloindoline structure in peptides[1,2]. The previous experiments in our laboratory demonstrated that KgpF exhibits remarkably broad substrate tolerance. This characteristic of KgpF enabled prenylation of more than 10^{14} types of artificial thioether macrocyclized peptides by a simple operation.

Using this library, ligands against multiple therapeutic target proteins were successfully obtained. These ligands exhibited strong affinity with Kd values of low nM level. In this talk, details about the design of the library, the *in vitro* selection experiments, and unique functionalities of the obtained bioactive pseudo-natural peptides will be described.



1) *Angew. Chem. Int. Ed.,* 55, 3596-3599 (2016). 2) *Org. Biomol. Chem.*, 14, 9639-9644 (2016).