Development of bioactive prenylated peptides that show enhanced cellular uptake efficiency

(*Graduated school of Science, The University of Tokyo*) ○Sumika Inoue, Rika Okuma, Yuki Goto, Hiroaki Suga

Keywords*:* Macrocyclic peptide; Prenylation

Macrocyclic peptides are promising candidates for bioactive compounds because they can interact with their targets in a robust and specific manner. However, their hydrophilic nature and larger molecular weight make them difficult to be internalized into the cell compared to small organic molecules. To circumvent this problem, increasing hydrophobicity by lipidation is known to be an effective approach to improve affinity with the cell membrane. In this study, we aimed to introduce prenyl moieties into peptides to facilitate their intracellular delivery.

For the method to introduce prenylation, we focused on the enzymatic modification of peptides found in the biosynthetic pathway of a cyanobactin. KgpF catalyzes dimethylallylation of tryptophan and is involved in preparation of kawaguchipeptin[1,2]. We employed KgpF to modify a variety of substrates and constructed a library containing over trillion prenylated peptides. From the resulting library, peptide ligands for Ce-iPGM (independent phosphoglycerate mutase from *C.elegans*) were successfully selected. One of the identified prenylated peptides showed low nM levels of binding affinity and inhibitory activity against Ce-iPGM, depending upon the prenylated structure.

To examine the intracellular localization of the peptide, microscopic and FACS analyses of cells treated with its fluorescent-labeled derivative were conducted. Compared to the control peptide without the prenyl group, the prenylated peptide showed higher cellular translocation efficiency. The labeled peptide overlapped with lysosomes in the microscopic images, suggesting uptake by endocytosis.

This presentation will describe the methodology used to develop the prenylated peptides and the observed functions of the resulting peptide.

[1] Parajuli, A, *et al.* (2016) *Angew. Chem. Int. Ed.*, **55**, 3596-3599.
[2] Okada, M, *et al.* (2016) *Org. Biomol.*, **14**, 9639-9644.