標的タンパク質阻害する非天然アミノ酸配列を移植した人工チオペプチドの開発

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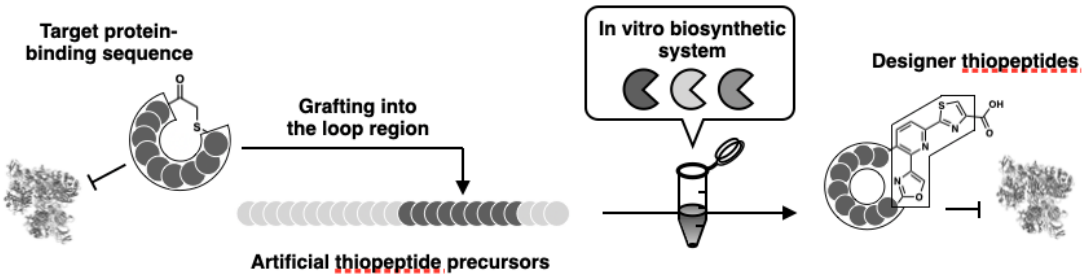
Development of designer thiopeptides with grafted noncanonical sequences inhibiting a target protein of interest ([1]*Graduate School of Science, The University of Tokyo*) ○Kakeru Narumi[1], Kyohei Miyairi[1], Yuki Goto[1], Hiroaki Suga[1]

Thiopeptides, a class of natural product peptides, commonly have characteristic backbone heterocycles such as azoles and ring-closing pyridine moiety. Because of their enhanced hydrophobicity compared to backbone amides, thiopeptides often show cell membrane permeability and inhibit intracellular targets. Therefore, thiopeptides have been utilized as promising candidates for drug discovery. However, the sources of bioactive thiopeptides have been limited to native natural products and their derivatives, and thus the development of thiopeptide drugs with the desired activity has required extensive screening and serendipity. Towards the on-demand design of de novo thiopeptides inhibiting proteins of interest, we aim to establish a system for the development of designer thiopeptides with artificial loop sequences targeting a specific protein.

Our group has previously reconstituted the biosynthetic pathway of a thiopeptide lactazole *in vitro* and demonstrated the production of various thiopeptide analogs containing artificial sequence compositions[2]. In this study, several artificial thiopeptide precursors, in which β-galactosidase- or SIRT2-binding sequences characterized by *in vitro* selection inhibitory cyclic peptides[3] are grafted into the loop region, were designed. One-pot expression and posttranslational modification of these chimeric precursors in the *in vitro* biosynthetic system led to the objective designer of thiopeptides. The resulting thiopeptides retained the designed inhibitory activity against the targets. This result opens a way to develop de novo thiopeptides with the desired bioactivity.

Keywords: Peptidic natural products; Peptide drugs; Posttranslational modification



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