論文の内容の要旨

Development of potent macrocyclic peptide inhibitors against cofactor independent phosphoglycerate mutase of parasitic nematodes

（寄生性線虫コファクター非依存性ホスホグリセリン酸ムターゼに対する大環状ペプチド阻害剤の開発　）

氏名　余　昊

Diseases caused by parasitic nematodes are serious public health problems in developing countries that affect millions of people worldwide. Treatments for parasitic nematode caused diseases, such as the lymphatic filariasis caused by Brugia malayi, have not been well developed to date. The enzyme Cofactor-independent phosphoglycerate mutase (iPGM) catalyzes the critical interconversion of 2-phosphoglycerate and 3-phosphoglycerate in the glycolytic and gluconeogenic metabolic pathways that are essential for the growth of nematodes, implicating iPGM as a potential drug target. However, iPGM is considered as protein with low “druggability”, and is thus not suitable for targeting with conventional small molecules. Since small molecules do not have sufficient binding interfaces to interact with the target proteins. Thus, alternative approaches are required for the discovery of iPGM inhibitors, which may be useful in the development of anti-parasite therapies. In this thesis, I report the discovery of macrocyclic peptide inhibitors against iPGMs via the Random non-standard Peptide Integrated Discovery (RaPID) system, Such an approach enables the rapid selection of high affinity iPGM-binders from a genetic code reprogrammed peptide library containing trillions of unique macrocyclic peptides.

In chapter 1, I introduce the situation of infectious diseases caused by parasitic nematodes, such as Lymphatic filariasis and current treatment for these diseases. The

limited effective drugs as well as increasing drug resistance call for identification of new drug targets and developing novel drug candidates. Subsequently, the characterization of cofactor-independent phosphoglycerate mutase (iPGM) is described and presents the potential of iPGM as a promising anti-parasite therapeutic target. Then, I discuss the challenges of traditional drug developing methods and introduce advantages of the RaPID system for peptide drug discovery.

In chapter 2, the development of macrocyclic peptides that bind to B. malayi iPGM is described as well as the determination of inhibitory activities. Several macrocyclic peptides are identified as B. malayi iPGM binders and exhibit inhibitory activity against iPGM orthologs. Furthermore, the structure activity relationship analysis is carried out on Bm-4 peptides by chemical modifications.

In chapter 3, an attempt at discovering C. elegans iPGM inhibitory peptides is discussed. Four macrocyclic peptides were selected and the binding affinity and inhibitory activity are evaluated. Ce-1 and Ce-2 are potent iPGM inhibitor with broad-spectrum inhibitory activity. The binding activity of Ce-2 is further studied via a series of chemical modification, including truncation, substitution and N-methylation. The binding site and inhibitory mechanism of macrocyclic peptide is elucidated by obtained co-crystal structure of cyclic peptide and C. elegans iPGM complex.

In the last chapter, the achievements in this study were summarized. Briefly, Discovery of such potent, selective, broad spectrum of macrocyclic peptide inhibitors gives new opportunities to develop non-druggable target against infectious nematode species and provide insights for rational drug design in future.