麻疹ウイルス膜融合タンパク質の変形阻害ペプチドの構造展開と阻害能評価

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Design and Evaluation of Derivatives of a Measles Virus Inhibitor Peptide that Inhibits Conformational Change of Measles Virus Fusion Protein ([1]*Graduate School of Engineering, The University of Tokyo*, [2]*Institute for Frontier Life and Medical Sciences, Kyoto University*) ○Ziwei Gao,[1] Jumpei Morimoto,[1] Jiei Sasaki,[2] Tateki Suzuki,[2] Takao Hashiguchi,[2] Shinsuke Sando[1]

MeV-F is a fusion protein located on measles virus (MeV) envelope. MeV-F undergoes a conformational change to fuse host cell membrane and virus envelope, which leads to virus infection. FIP (fusion inhibitor peptide)[1] binds to a hydrophobic pocket located at the region connecting the head and the stalk of MeV-F's pre-fusion state and stabilizes the pre-fusion state, which inhibits membrane fusion. FIP is potentially useful as an orally available drug candidate with small side effects because it binds to a protein unique to MeV and the molecular weight is small. However, the inhibitory activity of FIP is relatively weak and needs to be improved.

In this study, we optimized the chemical structure of FIP based on the co-crystal structure of MeV-F complexed with FIP[2] to design a membrane fusion inhibitor that has an improved inhibitory activity. In this presentation, the results of evaluation of the inhibitory activity and physical properties of designed FIP derivatives are shown.

Keywords : Peptide; Structure optimization; Measles virus; Membrane fusion inhibitor

MeV-Fは麻疹ウイルス (MeV) のエンベロープ上に存在する膜融合タンパク質である。MeV-Fは構造変化することにより、宿主細胞膜とウイルスエンベロープを融合し、感染を引き起こす。FIP[1]と呼ばれるペプチドは、MeV-Fの融合前状態の頭部と軸部分の間に存在する疎水ポケットに結合し、この構造変化を阻害することによりMeVの感染を阻害できる。FIPは、MeV特有のタンパク質を標的とすることと、分子量が小さいために、副作用の少ない経口投与薬候補として期待できる。しかしながら、FIPの膜融合阻害能は比較的弱く、改善する必要がある。

本研究では、より強力な膜融合阻害剤の創出を目標とし、MeV-FのFIPとの共結晶構造[2]に基づき、FIPの構造展開を行った。本発表では、設計したFIP誘導体の阻害活性評価の結果と物性評価の結果について示す。

1) Specific inhibition of paramyxovirus and myxovirus replication by oligopeptides with amino acid sequences similar to those at the N-Termini of the F_1 or HA_2 viral polypeptides. C. D. Richardson, A. Scheid, P. W. Choppin, *Virology* **1980**, *105*, 205.

2) Structures of the prefusion form of measles virus fusion protein in complex with inhibitors. T. Hashiguchi, Y. Fukuda, R. Matsuoka, D. Kuroda, M. Kubota, Y. Shirogane, S. Watanabe, K. Tsumoto, D. Kohda, R. K. Plemper, Y. Yanagi, *Proc. Natl. Acad. Sci. U. S. A.* **2018**, *115*, 2496.