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A proposal for peptide inhibitors to block the ligand-binding pocket of urokinase receptor: *ab initio* molecular simulations

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1. Introduction

A variety of proteases were found to play important roles in cancer invasion and metastasis. In particular, binding of urokinase-type plasminogen activator (uPA) to uPA receptor (uPAR) existing on the surface of a cancer cell is considered as a trigger for cancer invasions. It is thus expected that the blocking of the binding can inhibit cancer invasion efficiently. Based on the X-ray crystal structure of uPA-uPAR complex, it was elucidated which amino acid residues of uPA are important for the binding, and several peptides having these residues were synthesized as potent inhibitors [1].

In our previous molecular simulations [2,3], the specific interactions between uPA and uPAR were investigated at an electronic level by *ab initio* fragment molecular orbital (FMO) calculations. The results are comparable to the experiment [1] and highlight some important residues of uPA, which have strong attractive interactions with uPAR. In the present study, we constructed novel peptides composed of the important residues and investigated their specific interactions to uPAR by the *ab initio* FMO calculations, with solvating water molecules considered explicitly.

2. Results and discussion

We first constructed 6 types of peptides composed of 5~10 residues and docked each of them to the uPA-binding domain of uPAR by a protein-ligand docking program. These docked structures were fully optimized in water by classical molecular mechanics method, and binding energy between the peptide and uPAR was investigated by the *ab initio* MP2/6-31G method in FMO. Figure 1 shows the optimized structure of the solvated complex of uPAR with our proposed peptide. This peptide has the largest binding energy to uPAR among our proposed peptides. In addition, it was elucidated that Glu36, Glu134 and Glu135 residues of uPAR have large contribution to the peptide binding. Based on the results simulated, we furthermore mutated some residues of the peptide in silico and searched for the novel peptide inhibitors having larger binding affinity to uPAR. Such peptides are expected to be more potent inhibitors for cancer invasions. The details of the results will be shown at the conference.

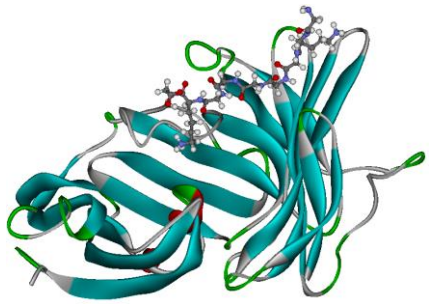

Fig.1 Our proposed peptide blocking the uPAR pocket

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