Development of high-affinity peptide ligands for serum albumin toward biomedical applications

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論 文 名　：Development of high-affinity peptide ligands for serum albumin toward biomedical applications
（バイオメディカル応用のための血清アルブミンに対し高い親和性を有するペプチドリガンドの開発）

区　　分　：甲

論　文　内　容　の　要　旨

Thanks to the particular molecular and biological characteristics that the human serum albumin (HSA) has, developing strategies to design HSA-based drugs have been extensively evolved. Whether conjugation of these drugs with HSA is through non-covalent, covalent or genetic engineering, the ultimate purpose is to enhance the pharmacokinetic profile of the compound. HSA is the major circulating protein in the blood which has a long half-life of about three weeks. HSA also has a great ability to carry various types of endogenous and exogenous compounds in the blood, including different drugs. Thereby, affecting their distribution, absorption, metabolism and excretion profile. In a vast variety of disorders such as tumor tissues and inflamed sites. On the other hand, among the therapeutic compounds, proteins and peptides are very promising due to their selectivity, efficacy, and safety. However, their rapid elimination by enzymatic degradation or renal clearance has hindered their usage. To address this issue and to utilize the benefits of HSA, development of a more general and simpler delivery system based on HSA is required. In this thesis, I approached this goal through two methods.

In chapter 2, I could successfully enhance the blood circulation ability of a small fluorescent probe by modification of a palmitoyl group on a folate-fluorophore conjugate in mice model. The alkylated probe maintained its specificity for binding to folate receptors which are overexpressed in many cancer cell types. Meanwhile, it induced an extended blood circulation through non-covalent binding to mouse serum albumin, compared with the probe lacking the alkyl group. It is supposed that this modified alkyl group could make non-covalent binding to the hydrophobic pockets of albumin. As a result, retaining the fluorescent probe for

an extended time in the blood and higher accumulation in the tumor region. This result can be promising for the development of small fluorescent probes in near-infrared imaging used in the intraoperative imaging.

In chapter 3, I reported a novel design of peptide-based ligand with a strong binding affinity to human serum albumin (HSA), which can be used as a tag to extend the blood circulation of the small size molecules. I designed these ligands with dual alkyl groups connected with a negatively charged spacer. By a competitive binding technique, it was found out that the designed dual alkylated peptides with the tuned and shorter spacer were able to specifically share the HSA's binding pockets 4 and 6 for fatty acids, with a significantly higher binding affinity than that of the single alkylated peptide. Additionally, Cy7 modified dual alkylated peptide showed higher retention in the mice blood circulation than that of a single alkylated peptide, suggesting higher binding affinity of the former type of peptide to mouse serum albumin. No crystal structure of mouse serum albumin has so far been reported. But based on amino acid sequential studies, essential residues for the binding of fatty acids are nearly entirely conserved among all species. Thus, we can expect a similar binding behavior from human serum albumin and mouse serum albumin.

The novel approaches and findings in this research, may provide new insights into the development of more straightforward methods to utilize the unique advantages of HSA. And in a broader sense, they can lead realizing of more efficient and cheaper medications for severe diseases.