Two strategies to improve the drug delivery efficiency: ligands for major histocompatibility complex class I and serum albumin

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論文内容の要旨

Drug delivery system improves the effect of drugs and reduces potential toxicity of drugs via different strategies. In this thesis, the author developed two strategies to improve the delivery efficiency for drugs in the blood, based on the targeting of cell surface molecule and the blood half-life extension by using an endogenic carrier protein, respectively.

Recently, major histocompatibility complex class I (MHC-I) has been found to be overexpressed on the cell surface in various autoimmune diseases. In addition, a peptide exchange reaction has been reported to happen between exocytotic peptides and peptide/MHC-I complexes on the cell surface. These facts indicated that MHC-I can be a target molecule by using exocytotic peptides as ligands.

In chapter 2, the author designed ligand peptides for a specific MHC-I on the cell surface. To design the ligand peptides, reported antigen peptides for each MHC-I molecule with high binding affinity were used. From the crystal structure of the peptide/MHC-I complexes, a modifiable residue which does not interaction with the surrounding MHC-I residues was selected and was replaced with a lysine with an ε-amine group modified with functional molecules. The designed ligand peptides successfully bound to cells expressing the corresponding MHC-I molecules via exchange of peptides bound to the MHC-I. The author also demonstrated that the peptide ligands could be used to transport a protein or a liposome to cells expressing the corresponding MHC-I. The present strategy may be useful for the targeted

delivery to cells overexpressing MHC-I, which have been observed autoimmune diseases.

Human serum albumin (HSA) has been utilized as an endogenic carrier for various drugs. These drugs utilize hydrophobic pockets of HSA by modifying a fatty acid on drugs as a ligand for HSA or a covalent bond formation of maleimide group modified on drugs with cysteine 34 (Cys34) of HSA. However, it was difficult to strike a balance between stable binding to HSA for long blood-half and drug release from HSA to show bioactivity.

In chapter 3, a ligand was designed to bind to HSA via both disulfide bond and hydrophobic interaction. The ligands are composed of a thiol containing amino acid (cysteine or penicillamine), an oligoethylene glycol linker and an alkyl chain. The ligands were homo- or hetero-dimerized by disulfide bond formation to react with Cy34 by disulfide exchange reaction. The author showed that pre-organization of the ligands on HSA via binding through alkyl chain is a prerequisite for disulfide bond formation with Cys34. The ligand bound to HSA could be released from HSA in the reductive condition due to the cleavage of the disulfide bond with Cys34. These ligands are expected to be used to prolong the blood half-life of conjugated drugs by binding to HSA, while the ligands enable slow release of the drugs via the thiol exchange reaction with endogenic thiol compounds.

In chapter 4, the author summarized the results and put forward the perspective for the future development of this research.