Ligand -mediated Coating of Liposomes with Serum Proteins for Biomedical Applications

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https://doi.org/10.15017/1931748

出版情報：Kyushu University, 2017, 博士（工学）, 課程博士
バージョン：
権利関係：

（様式３）

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論 文 名　：Ligand-mediated Coating of Liposomes with Serum Proteins for Biomedical Applications
（リポソームの血中安定化を指向したリガンド介在型血清タンパク質被覆法の開発）

区　　分　：甲

論　文　内　容　の　要　旨

This thesis proposes new strategy of liposome surface modification of serum proteins, which is potentially useful for drug delivery. Liposome surface modification has grown extensively, and improved liposomes for clinical application by enhancing the stability to prolong the blood residence time and specificity to target cell to deliver the drugs. Two major serum proteins, human serum albumin and immunoglobulin G (IgG), show extraordinary long blood circulation time, and have been utilized for exploiting of protein-based drug. To introduce the advantage of the proteins into liposomes, serum albumin or IgG-modified liposome have been developed. Most of liposomes coated with serum proteins are covalently immobilized, which cannot circumvent the deterioration of the proteins' characteristics and takes time for production. On the other hand, ligand-mediated coating of surface is strong and has been expected to modulate the denaturation of the proteins. Furthermore, abundant endogenous proteins can be utilized for in situ coating after administration. In the present thesis, the author developed ligand-mediated coating method for serum albumin or IgG-coated liposome.

In Chapter 2 and 3, serum albumin-coated liposomes were exploited. Among numerous ligands of serum albumin, the author selected two types of ligands. The first one was bilirubin, which is known the have the highest binding affinity among the reported ligands. The coating of liposome with serum albumin and the reversibility of the coating were successfully monitored. However, it was found that the serum albumin-binding ratio to bilirubin on liposome surface was lower than expected. This relatively low binding ratio may result from the hydrophobic nature of bilirubin. Then, the second one was alkyl chains. The author used three types of alkyl chains with different chain length with or without terminal negative charge, and achieved coating of liposome surfaces with serum albumin via the ligands. A relatively short alkyl ligand or a long alkyl ligand with terminal carboxylate could be exposed on the liposome surface without causing aggregation of the liposomes and these ligands could subsequently bind HSA to significantly improve the colloidal stability of the liposomes. The resulting HSA-coated liposomes were as inert as conventional PEGylated liposomes in terms of macrophage recognition. This HSA coating has a possibility to improve the stability of the liposomes in blood for drug delivery system.

In Chapter 4, the author proposed IgG-coating of liposome by using Fc-binding peptide. The author used Fc-III peptide as a Fc-binding ligand. To modify the peptide onto the liposome surface, Fc-III was palmitoylated on its N-terminus. The liposome containing palmitoylated Fc-III was successfully coated with IgG. The author examined the recognition of IgG coated on the liposomes toward cell surface receptors. The anti-CD20-coated liposome bound to human B lymphoid cell line overexpressing CD20. In contrast, the IgG-coated liposome was not recognized by macrophage expressing FcγRs, which bound to Fc regions. This strategy may enable coating of the liposome with endogenous IgG in blood after injection and provide stealth characteristics to the liposomes.

The ligand-mediated coating of liposomes proposed here will extend the current liposomes technology. The author believe that this strategy has a potential to clinical applications because it enables in situ coating.