Form 3

Abstract of Thesis

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Title	Studies on Characterization of Hydration State of Layer-Modified Lipid Membrane toward Design of Self-Assembly Drug （自己組織化薬の設計を目指した表層修飾脂質膜の水和状態評価に関する研究）

Abstract of Thesis

Lipid membrane can work as new target for functional molecules, which make it possible to modulate cellular functions by regulating its self-assembled bilayer structure. Regulation of self-assembly properties is also important to optimize its performance as drug delivery system (DDS). In this study, several guest molecules were utilized to modify lipid membrane at different region from hydrocarbon chain region to surface. The effects of these guest molecules on lipid membrane properties were investigated. Especially the hydration state of modified lipid membranes was mainly characterized to clarify how the extraneous molecules modify the hydration state of lipid membrane. The findings obtained are expect to be applied in optimizing the prodrug based self-assembly DDS (SADDS) by reasonable molecular structure design.

In chapter II, Quercetin (QCT) was utilized to modify the lipid membrane hydrocarbon chain region. Based on Raman spectra results, it was found that QCT could show great effect on the hydrocarbon tail region of lipid membrane, and hydrocarbon chain length and the level of unsaturation played an important role in determining the effect of QCT. For QCT, the regulation of hydration state of membrane lipid was achieved by changing the carbon chain packing density. This packing density variation of lipid membrane also affected on free radical diffusion within membrane.

In chapter III, the hydration state of lipid membrane interfacial region was modified by 2-hydroxyoleic acid (2OHOA). The effect of 2OHOA on (dipalmitoylphosphatidylcholine) DPPC and (sphingomyelin) SM lipid membrane structure and hydration property were studied. Although there was no significant difference in overall structure between 2OHOA modified DPPC and SM lipid membrane, only 2OHOA-incorporated SM membrane polarity showed high sensitivity to pH condition and salt concentration. The reason for this difference can be attributed to the hydrogen bonding interaction of 2OHOA with SM molecules. Therefore, it is concluded the hydration state of interfacial region can be modified by regulating the hydrogen bonding network formed by lipid molecules.

In chapter IV, Resveratrol (RES) was utilized to modify the surface polarity of heterogeneous lipid membranes, the effects of RES on lipid membrane properties were evaluated by multi-focal fluorescent probes. In each model membrane system, the incorporation of RES dramatically dehydrated the membrane surface, and this phenomenon was attributed to water species transfer induced by hydrogen bonding formed with hydroxyl group of RES.

In chapter V, polyamidoamine amphiphilic dendrons (ADs) with multiple amide and amine groups were utilized to achieve control of superficial hydration shell modification of membrane. In this chapter, the structure and their properties of lipid/AD coassembly were characterized, and confirmed the formation of hydration shell on lipid membrane surface after G1-AD modification.

Above studies has indicated that the headgroup regulation and hydrocarbon chain density regulation are main factors to regulate the membrane hydration state. In chapter VI, the method to prepare SADDS with different hydration degree was proposed. The aryl carboxylic acid Oxaprozin was selected as a model molecule to design fatty acid-like Oxa-lipid, which is available for the control of the headgroup by pH condition and the packing density by different hydrophobic chain length.

様式７

論文審査の結果の要旨及び担当者

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論文審査の結果の要旨

生体膜機能を活用することを主目的として，生体膜そのものやモデル生体膜(リン脂質2分子膜)が有する特徴を定量的・体系的に評価する手法が数多く報告されている．一般的なものは蛍光分子プローブ法であり，近年では，同位体ラベルNMR法，表面増強ラマン分光法，など，膜構成分子の状態を高感度に検出し，分子集合体としての特性を解析する手法としての有効性が示されている．一方で，モデル生体膜(リポソーム，ベシクル，平面膜など)は高分子量医薬品のDDSベクターとして活用されており，表層デザイン戦略を確立することが必要とされている．DDS応用の際，リン脂質表層に局在する官能基や脂質膜疎水部の不飽和度など，モデル生体膜を構成するリン脂質そのものの特長を加味し，それらの種類・濃度を制御する手法が一般的であるが，近年では，主役である高分子量医薬品分子(タンパク質や核酸)が直接に接し，その構造機能を制御しうる膜表層の水和状態に着目した研究が増加している．本学位論文では，脂質膜表層から内部に至る各層(layer)に各種外乱分子を導入し，分子集合体としての膜特性を制御することを目的とした新奇な手法(layer-modified法)が提案されている．第１章では，モデル生体膜のDDS利用法および脂質膜の各階層を解析する手法に関する背景を調査した．脂質膜の各階層(multi-focal layer-modification)の修飾を企図して，第２章では疎水性(hydrocarbon)領域に配向する分子(quercetin)，第３章では親疎水性界面(glycero骨格)領域に配向する分子(2-hydroxyoleic acid)，第４章では親水性官能基(phosphate)領域に配向する分子(resveratorol)，第５章では最表層(choline)領域に配向する分子(polyamidoamine amphiphilic dendrons)を脂質膜に導入し，既存解析法(蛍光プローブ法，LB膜解析法，ラマン分光法など)を用いて，脂質膜特性(特に，水和状態)の変化を系統的に検討した．第６章では，前章までの知見に基づいて，脂質膜の各階層に外来性分子を導入することで，階層特異的に焦点を当てて脂質膜特性を制御する一般的手法(layer-modified法)を明示した．さらに，分子集合性医薬品デザインへの応用を志向して，モデルPro-Drug(疎水化oxaprozin)が形成する自己集合体の基礎物性の検討結果に基づいて，効率的な医薬品送達モデル(生体膜界面濃縮，エンドソーム，薬剤送達 ほか)を提案し，それにより，layer-modified法の妥当性を示した．よって，博士（工学）の学位論文として価値のあるものと認める．