Advances in Planar Lipid Bilayers and Liposomes

Volume 13

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ADVANCES IN PLANAR LIPID BILAYERS AND LIPOSOMES

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Preface

Volume 13 involves the chapters describing the mechanical properties of lipid bilayer membranes and protein–lipid interactions, lipid and membrane dynamics in biological tissues, membrane skeleton reorganization, photovoltaic solar energy conversion in biomembranes, multiparametric fluorescence approach in biomembrane experimental studies, and interactions between osteoblasts and titanium surface of implants. I would like to express my gratitude to all authors contributing their chapters, that is, to Profs. and/or Drs. S. Yoshida, K. Koike, T. Hianik, D. Kabaso, R. Shlomovitz, T. Auth, V. L. Lew, N. S. Gov, F. T. Hong, A. A. Heikal, E. Gongadze, Š. Perutková, V. Kralj-Iglič, and U. van Rienen. I also very much appreciate the continuous support of Ben Davie from Elsevier Office in London together with its coworkers from Elsevier's Chennai Office in India, Paul Prasad Chandramohan, Sunita Sundararajan, and Vijayaraj Purush. I would like to use this occasion to express my gratitude to the following members of the Editorial Board of APLBL: Prof. Sylvio May, Prof. P. B. Sunil Kumar, Prof. Nir S. Gov, Prof. Tibor Hianik, and Dr. Michael Rappolt. Special thanks to the previous editor Prof. Angelica Leitmannova Liu.

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CHAPTER ONE

Lipid and Membrane Dynamics in Biological Tissues—Infrared Spectroscopic Studies

Satoshi Yoshida[1,*] *and* Kenzo Koike[2]

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Abstract

Functions of cell bilayer membranes are closely linked to dynamics and behavior of network of membrane components including lipids, proteins, and glycans. It is important to investigate the role of membrane components in the membrane functions without damage of the network of components. This is the reason why noninvasive and nondestructive analyses are so important for the study of the

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intact membranes and tissues. Vibrational spectroscopies including near- and mid-infrared absorption and resonance Raman scattering spectroscopies are useful for these purposes. In this chapter, we summarize the application of infrared spectroscopy to studies of lipids and bilayer membrane dynamics in biological tissues, and to the research for diagnosis of human diseases.

Abbreviations

18-MEA	18-methyl-eicosanoic acid
AGEs	advanced glycation end products
ATR	attenuated total reflectance
CERs	ceramides
CHOL	cholesterol
DEPE	1,2-dielaidoyl-*sn*-glycero-3-phospho-ethanolamine
DHA	docosahexaenoic acid
DMPA	1,2-dimyristoyl-*sn*-glycero-3-phosphate sodium salt
DPPC	dipalmitoylphosphatidylcholine
ESG	esterified sterylglucoside
ESI-MS	electrospray ionization-mass spectrometry
FFA	free fatty acid
FTIR	Fourier-transform infrared
GAGs	glycosaminoglycans
GalCer	galactocerebroside
GlcNAc	*N*-acetylglucosamine
HDL	high-density lipoprotein
IR	infrared
LDL	low-density lipoprotein
MALDI-TOF-MS	matrix-assisted laser desorption ionization time-of-flight mass spectrometry
NMF	natural moisturizer factor
NMR	nuclear magnetic resonance
PCA	principal component analysis
PLS	partial least square
POPC	palmitoleic phosphatidylcholine
SC	stratum corneum

1. Introduction

Cell membrane and tissue lipid dynamics are playing important roles in the life of all organisms on the earth. Especially, the cell membranes with phospholipid bilayer have mainly two functions (1) clear separation of the

inner cell space from the outer world and (2) mediation of signal transduction and communications between the inner and outer spaces. These important functions of cell membranes are based on various biomolecular components, such as lipids (including fatty acids), proteins (enzymes, receptors, transporters, channels, and cytoskeletons), and glycans, and their interactions.

Functions of cell membranes are closely linked with dynamics and behavior of network of membrane components, such as lipids, proteins, and glycans with the aid of minerals and other nutrients. Thus, it is important to investigate the role of membrane components in the membrane functions without disruption of membrane integrity and without damage of the network of components. This is the reason why noninvasive and nondestructive analyses are so important for the study of membrane components in the intact membranes.

For noninvasive and nondestructive analyses of membrane systems, vibrational spectroscopies including near- and mid-infrared absorption and resonance Raman scattering spectroscopies are useful for these purposes. Vibrational spectroscopy can reveal the characteristics and interaction with the environment of biomolecules. Basically, the mid-infrared spectroscopy is based on the net changes of dipole moment of the molecules ("IR-active"), whereas the Raman spectroscopy is based on the change of electric polarizability of the molecules ("Raman-active"), and thus these spectroscopies are complementary techniques for studies in chemistry.

The mid-infrared absorption and Raman scattering spectroscopies are frequently used to study the interaction between lipids and proteins or glycans in the cell membrane, and this is due to the evidence that the energy level of hydrogen bonding or some interactions is comparable to the infrared energy level, and the interaction change between functional groups of membrane biomolecules (e.g., receptors, channels, glycoproteins, and glycolipids) and the surrounding water or lipid or protein molecules may be detectable in the infrared region.

Vibrational spectroscopy can reveal not only the characteristics of specific functional group, but also the mixture of many functional groups. As a matter of fact, the change of membrane dynamics may be in part the result of change of biomolecular networks in the membrane. This is because the application of statistical multivariate analysis or chemometrics to vibrational spectroscopy is useful and important for the noninvasive analyses of cell membranes, food staffs, and human tissues.

In the multivariate analysis or chemometrics for vibrational spectroscopy, the principal component analysis (PCA) and partial least square (PLS) regression analysis methods are frequently used for classification or categorization of phenomena, such as membrane dysfunction, or predication of change of factors which are, for example, some disease-related lipids and fatty acids. These statistical methods may provide vibrational

spectroscopy—the chance to supersede the diagnosis of diseases with invasive clinical tests and destructive tests of food staffs.

The vibrational spectroscopy has been widely applied to the diagnostic analysis of diseases and nondestructive analysis of food staffs; however, at present there have been few vibrational spectroscopic techniques used as golden standard methods for diagnostic analyses. Usually biochemical analyses of blood or other body fluids have been used for the diagnosis as standard methods, and only one or a few specific factors could be measured in one shot of detection. For example, total cholesterol (CHOL), LDL, HDL, and triglycerides were mainly measured for diagnosis of hyperlipidemia which would be linked, in some cases, to complex metabolic diseases. Some complex diseases such as diabetic diseases and atherosclerosis may have complex pathogenic mechanisms with many onset factors and thus many biomarkers.

To realize those complex diseases and diagnosis, the technique which would detect many factors in a short time noninvasively by one shot of measurement would be very useful, and for this purpose the vibrational spectroscopy—especially mid-infrared spectroscopy—would be suitable because it can detect the change of properties of cell bilayer membranes including proteins, lipids, and glycans simultaneously, and actually the near- and mid-infrared spectroscopy as well as Raman scattering spectroscopy may have a great potential in the clinical diagnostics field.

In this chapter, we summarize the advances of infrared spectroscopic techniques in the study of cell membranes and lipids and their interactions with other biomolecules in relation to the diagnosis of human diseases.

2. Historical View of Vibrational Spectroscopic Studies on Lipids and Membrane Dynamics in Biological Tissues

Application of vibrational spectroscopy, especially mid-infrared spectroscopy, to the studies of cell membrane and lipids has a long history and has provided a lot of data concerning to the study of membrane and lipid dynamics in human tissues.

2.1. Membrane Fluidity

Infrared spectroscopy could reveal the fluidity change of the cell membranes and liposomes with measuring the methylene CH stretching mode of the membrane fatty acyl chains [1,2]. Membrane fluidity could be measured also by other methods, such as using electron spin resonance and fluorescence probes [3], and the viscosity change corresponding to the capability of

moving of fatty acyl chains in the membrane was detected as a kinetic parameter of microenvironment of the probes. On the other hand, the measurement of membrane fluidity by infrared spectroscopy may show the extent of packing of membrane acyl chains, or in another words "softness of the membrane" which is a static parameter of macroenvironment.

Actually, the change of membrane fluidity may be measured by the change of infrared absorption peak position for methylene CH symmetric stretching mode at around 2850 cm^{-1} [1,2] as well as NMR measurement [4]. In the fluidity measurement, the peak shift to lower wave number direction indicated that the membrane became harder or ordered in the lipid network structure, whereas the shift to higher wave number direction indicated softer or disordered [5]. The infrared spectroscopic analysis could be used for elucidation of phase behavior of long-chain phospholipid membranes [2].

In lipid bilayer membranes, acyl chains in the lipids are interacted with each other by the van der Waals or London forces. When the interaction among methylenes was increased with the increase of packing of the membrane acyl chains which were attracted with each other by London forces, methylene CH bond force constant might be decreased. This would shift the CH symmetric stretching mode-originated infrared absorption peak to the lower wave number (energy) direction, for example, a shift from 2853 to 2852 cm^{-1}, indicating hardening of the membrane and usually observed when the temperature was decreased from 37 to 10 °C for pig brain microsomal membranes (unpublished result).

In another case, the Fourier-transform infrared (FTIR) spectroscopic analysis of lipid O=P=O, C=O, and C–H vibrational bands of POPC/CHOL (palmitoleic phosphatidylcholine/cholesterol mixture) liposomes revealed an increase in the conformational order of the acyl chains at or close to the predicted critical cholesterol molar fractions [3]. Here, the shift of methylene infrared absorption peak was observed from 2851.2 to 2850.7 cm^{-1} when the fraction of cholesterol was increased from 0% to 40%. This indicated that the insertion of cholesterol to POPC model membrane contributed to the increase of packing of membrane acyl chains.

For measurement of membrane fluidity in the biological tissues such as artery, it would be difficult to use probe methods (using fluorescence anisotropy measurement and electron spin resonance spectroscopy) because the probe methods would require the insertion of external probe to the tissue membranes and the suitable insertion of probe might be practically impossible to the arterial membrane. Infrared spectroscopy provides a technique that does not require the insertion of probes, and this is especially advantageous for measurement of biological tissues.

Actually, the application of FTIR for measurement of mouse pulmonary artery was reported [6] and the change of conformational disorder (fluidity) in the artery membrane lipids could be detected. In this case, the arterial

tissue was sandwiched by CaF_2 disks and the transmission FTIR absorption spectrum could be measured. In this report, the average conformational disorder in membrane lipids in the pulmonary artery *in situ* was increased by the treatment of monocrotaline which was a toxic alkaloid and caused early pulmonary endothelial injury with gradual development of pulmonary hypertension. Moreover, the membrane fluidity of carotid tissue of spontaneously hypertensive rat could also be measured *in situ* [7], and the membrane fluidity was increased in the hypertensive rat carotid subjected to anoxia, but not in the control rat. In the carotid or pulmonary arterial tissues, the increase of membrane conformational disorder would be linked to vulnerability of the tissue membrane.

2.2. Hydration of Membrane

The state of hydration of membrane surface may affect the hydrolytic activity in or on the surface of membrane, and the hydration may be closely related to the presence of glycans on the membrane, especially glycosylated lipids and proteins. Actually, it was reported that the interfacial properties of cell membranes were important and phospholipase A_2 activity was influenced by hydration (or in another word, water activity) of the membrane surface [8–10], and thus the inflammation was affected.

Hydration state around carboxyl and phosphate groups may be affected by the presence of polyhydroxy compounds (such as glycans) or by changing the chemical groups esterified to the phosphates, mainly choline, ethanolamine, or glycerol. Thus, surface membrane properties, such as the dipole potential and the surface pressure, are modulated by the water at the interphase region by changing the structure of the membrane components [10–13].

The hydration or dehydration of membrane surface could be measured by FTIR using the absorption of hydroxy (–OH) and carboxylate (–COO–) groups which would be changed by the change of hydrogen bonding with water around the residues on the membrane surface. It was reported previously [8] that nondestructive FTIR analysis could detect the modification of rat brain microsomal membranes and these modifications of brain microsomal membranes were dependent on the dietary fatty acids and learning behavior. In this report [8], FTIR spectral differences for brain microsomes were observed mainly in the absorption bands of fatty acyl ester at around 1730 cm^{-1} (*sn*-2 position), phosphate ester and oligosaccharides in the range of 1050–1100 cm^{-1}. The infrared band of fatty acyl ester at the *sn*-2 position in the microsomal membrane shifted to a higher wave number position (1731 cm^{-1}) in the perilla oil-diet group (α-linolenic acid-rich) than that in the safflower oil group (α-linolenic acid-deficient) at 1727 cm^{-1} after the learning behavior, suggesting a difference between both groups in hydrogen bonding of the fatty acyl ester with water. Without learning behavior, both groups showed similar ester absorption at *sn*-2 position (1729