

# **Current Topics in Membranes and Transport**

**VOLUME 17**

## **MEMBRANE LIPIDS OF PROKARYOTES**

*Guest Editors*

**Shmuel Razin  
Shlomo Rottem**

**ACADEMIC PRESS**

# Current Topics in Membranes and Transport

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**VOLUME 17**

**Membrane Lipids of Prokaryotes**

*Guest Editors*

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*To the Memory of Yuval Razin*

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# Foreword

Profligacy rather than economy characterizes the design of naturally occurring membrane lipids, or so it would appear from what we know today. If one were to define a structural denominator common to all components of membrane lipid bilayers, would it be more specific than the amphipathic nature or the inherent competence to form closed vesicles? Diversity seems to be the rule. In fact, and this is rarely mentioned, cell membranes containing a single phospholipid species do not seem to exist. It is true that one type usually predominates, e.g., phosphatidylcholine in eukaryotic membranes and phosphatidylethanolamine in bacteria, but they alone seem to be inadequate as matrices for the varied functions membranes are believed to perform. Is it possible that bilayer asymmetry is essential for biological function and that for this reason alone membrane phospholipids are not limited to a single species? Perhaps this intriguing question could be answered if it were possible to create viable bacterial mutants containing phospholipids of a single type.

In view of the compositional complexity of natural membrane lipids, it is remarkable that chemically homogeneous liposomes mimic many natural membrane properties, including transport, phase transitions, or effects on membrane-associated enzymes. Clearly there must exist a wide variety of membrane-associated phenomena expressed only in cells which studies with single component model membranes cannot reveal. In the future, attention will have to be paid increasingly to this question, i.e., to the role of the minor membrane phospholipids and their involvement in regiospecific functions. Perhaps bulk phase properties as a function of phospholipid structure have been unduly emphasized.

Prokaryotic membrane phospholipids, though by no means simple in composition, are nevertheless much less complex than their eukaryotic counterparts. As for fatty acyl structures, the  $C_{16}$  and  $C_{18}$  saturated and monounsaturated fatty acids predominate, but with rare exceptions di- and polyunsaturated fatty acids are absent. A departure from this general pattern may signify a specialized function. Olefin-derived cyclopropane acids are found in late log and stationary phase *Escherichia coli* cells. Yet the significance of these branched acids is by no means clear. *Escherichia coli* mutants lacking the requisite methyl transferase do not seem physiologically impaired. The need for relatively low-melting long-chain acids is met differently by *Bacillus* species. They produce iso- and anteiso acids

even though they have the mechanisms for introducing olefinic bonds into saturated acids. It is also worth noting that some bacteria generate olefinic acids by the anaerobic dehydration pathway while others use oxidative desaturation, the universal eukaryotic pathway.

A striking departure from the usual fatty acid patterns is found in cells living in extreme environments (temperature, acidity, ionic strength), e.g., extreme halophiles, thermophiles, and also the organisms recently classified as Archaeobacteria. Instead of the common fatty acids, they employ as hydrophobic chains phytanyl residues in stable ether linkage. Even more remarkable, in the form of diphytanyl diglycerol tetraethers they have the proper dimensions and therefore the potential for spanning the membrane bilayer. If they did they would in essence function as lipid monolayers. The exotic structures of the phytanylether lipids appear to represent alternative solutions to membrane rigidity or stability since their presence correlates with the absence of the peptidoglycan cell wall.

It has been generally true for phospholipids from all sources that saturated fatty acids are esterified at C-1 and unsaturated fatty acids at C-2 of the glycerol moiety. Yet there are exceptions to this rule. Positional inversion in the phospholipids of clostridia has long been known and more recently observed in certain mycoplasmas. Physiological consequences of the nonrandom fatty acyl esterification sites and its inversion have not been recognized and therefore remain unexplained.

In bacteria phosphatidylglycerol and phosphatidylethanolamine are the most common phospholipids, whereas phosphatidylcholine is only rarely found, a pattern which distinguishes prokaryotic membranes most strikingly from eukaryotes. Clearly, the bulk and the net charge of the polar head group cannot be trivial but must play a crucial role in the interaction between the cell envelope and the external milieu. If the subject of phospholipid specificity has remained almost entirely unexplored the reason is undoubtedly that it is rarely absolute and difficult to demonstrate. For the further exploration of this important subject prokaryotes are clearly the cells of choice. Modulation and control of the environment and mutant selection are more readily realized than with eukaryotic cells.

Phospholipid biosynthesis is reasonably well understood today, at least the chemistry of the pathways is. The respective enzymology is much less advanced since the component enzymes are membrane-associated and therefore more refractory to purification. For studies of prokaryotic phospholipid biosynthesis, *E. coli* has for obvious reasons been the organism of choice. However variations from the *E. coli* pathway are to be expected and have in fact been encountered earlier in clostridia. For mycoplasma and achleoplasma phospholipid biosynthesis there is at best fragmentary information.

Equally or even more uncharted territory is the regulation of phospho-



lipid biosynthesis in both prokaryotic and eukaryotic cells. It is perhaps not too unreasonable to predict that the control points and the identity of the modifier molecules for the two cell types will be unrelated. Certainly the physical environment and the stimuli to which the respective cells respond have little in common. How little we know in this area is illustrated by the fact that several decades after the discovery of the phenomenon proper, we still do not know how bacterial cells regulate the synthesis of more or less unsaturated phospholipid in response to temperature changes. Regulation may occur at the stage of unsaturated fatty acid synthesis or glycerophosphate-acyl-CoA transacylation. Conceivably more than one of the component steps is under control and perhaps by the same controlling molecule. For microorganisms a compelling case can be made that phospholipid biosynthesis is coordinated with membrane assembly and macromolecular synthesis. Indeed, substantial evidence exists, at least from *in vitro* studies, that the magic spot nucleotides (ppGpp) are negative effectors for several of these processes.

Sterols are rarely mentioned in conjunction with discussions of prokaryotic lipids, and understandably so. Sterol-producing or -requiring prokaryotes are exceedingly rare, and this fact seemed to support the view that molecules of this type were not invented prior to the appearance of eukaryotic cells along with intracellular membrane-bound organelles. This, as so many generalizations in biology, had to be abandoned even though sterols probably play, whenever they occur, a much more restricted and less specific role in bacteria than they do in higher cells. The formation of the sterol structure in amounts sufficient to affect membrane properties has been observed only in the instance of *Methylococcus capsulatus*. But even in this organism the sterol pathway stops short of full development. Equally unique among prokaryotes is the absolute sterol requirement of *Mycoplasma* species. Studies with these small bacteria have nevertheless provided useful information on sterol structure-function relationships that may be of more general significance even for eukaryotic systems.

It has come as somewhat of a surprise that the sterol precursor squalene is quite widely found in prokaryotes including the anaerobic Archaeobacteria. Moreover, squalene transformation to pentacyclic triterpenes of the hopane type, traditionally higher plant products, is not uncommon in these organisms. It appears that these early trials of nature to cyclize squalene—without intervention of oxygen—produced molecules that share certain structural and perhaps also functional features with the sterols. Evolutionary “tinkering” with squalene is in fact observable in *Methylococcus capsulatus*, an organism which produces both lanosterol derivatives from squalene epoxide and pentacyclic triterpenes from squalene.

During its relatively short history prokaryotic lipid biochemistry has produced a wealth of novel and often unique information. This volume impressively demonstrates the viability and future promise of this field. The discovery of new structures is likely to continue and with less labor than in the past in view of the powerful analytical methods now available. Progress may come more slowly and may be less straightforward in the elucidation of membrane structure–function relationships. Yet this is the area of greatest challenge.

Success, whenever it comes, should bring great rewards, including perhaps a better understanding and rationalization of bacterial systematics and phylogeny.

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# Preface

The relative simplicity of prokaryotic cells has made them useful in the study of numerous aspects of cellular biology, including membrane structure and function. Moreover, the availability of techniques for genetic manipulation has made possible the controlled alteration of membrane lipids and proteins in ways not yet possible in the case of eukaryotes. A striking example are the studies that provided the first direct demonstration of the bilayer organization of lipids in biological membranes, evidence for which was obtained by changing the fatty acid composition of the plasma membrane of *Acholeplasma laidlawii* and *Escherichia coli*. Other studies utilizing prokaryotes have elucidated the physical state and turnover of membrane lipids and their interrelationship with structural and catalytic membrane proteins. Similarly, our understanding of the pivotal role played by cholesterol and congeners in membrane structure and function—a major area of interest for eukaryotic cell membrane research—owes much to the studies of bacterial membranes.

Prokaryotic membrane lipid research also has intrinsic interest. Examples are the lipopolysaccharides of gram-negative bacteria, complex molecules that exhibit a wide spectrum of biological properties. The unique lipids found in bacteria that live in extreme environments, such as the Dead Sea, constitute another area of recent research, since they may provide clues to the understanding of how living organisms have adapted to harsh environments.

The wide interest in prokaryotic membrane lipids has given rise to many scientific reports and specialized reviews. This volume is the first to have assembled in one source descriptions of the significant advances made in prokaryotic lipid research during the past decade. In addition to providing systematic coverage, we hope the articles in this volume will also give rise to further research. Thus this work will not only serve as a reference source for scholars, teachers, and students, but will stimulate investigators to attempt solving the many problems that remain.

The help of expert colleagues was indispensable in collating current knowledge covering such diverse fields as membrane and lipid biochemistry, microbiology, and cell biology. Our special thanks are due to the contributors for their willingness to help make this book a reality.

SHMUEL RAZIN  
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