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Preface

A surface view on membrane structure, dynamics and applications

During the past few years, a whole collection of new methods has been developed permitting the study of natural and model membranes with details never achieved before. Application of single-molecule fluorescence or scanning force microscopies has revealed a picture with unprecedented resolution on the organization of lipids and proteins in membranes, including in some cases access to time-resolved aspects. Different techniques have been developed to attach membranes in solid supports and make them available for a detailed space-resolved exploration of features such as lateral organization and packing, thickness, lipid and protein dynamics, lipid-protein interactions, etc. The experimental approaches described in the reviews collected in this special issue have in common that they permit characterization of properties classically explored by surface chemistry, providing in a sense a view of lipid biomembranes as "functionalized" surfaces, optimized for many different types of processes. The concept of "surface" is somehow inherent to biomembranes but has been poorly considered when studying membrane systems in bulk. This issue assembles articles dedicated to many of these approaches, providing a perspective of the possibilities and approaches available today when studying biomembranes from a surface point of view.

A complementary aspect that is spread over the different articles in this issue is the potential of such membrane surface approaches to develop new biotechnological applications, derived from the possibilities to attach membranes at the surface of different devices, including the design and optimization of high-throughput biosensors.

A first group of reviews has been devoted to the study of different aspects of membrane structure using surface techniques applied on membranes attached onto solid supports. The article by Giocondi et al. has revised the use of atomic force microscopy (AFM) to characterize lateral organization of membranes, with particular attention to the detection and analysis of compositionally differentiated membrane domains. Much literature has appeared in the past few years on the potential existence of the so-called "rafts," membrane regions enriched in phospholipids with saturated acyl chains and cholesterol, which were originally defined by their supposed resistance to solubilisation by detergents. Phase segregation and co-existence in phospholipid membranes have been a matter of interest for physical chemists for decades, but the hypothesis that segregated membrane domains could define a regulated level of membrane structure and function in cells was what brought the interest of studying lateral membrane organization to biologists and increased enormously the impact of the research in this topic. Surface scanning microscopy techniques are among the few with the potential to resolve differences in membrane thickness in the order of 1 Å and below, provided that the membrane is attached onto an atomically flat support. Differences in thickness in this order of magnitude permit detection of segregated membrane regions without the introduction of spurious probes that could perturb by themselves the distribution of lipid and protein molecular species. Another important advantage compared with the classical observation of phase-segregated membranes under optical microscopy, is that AFM extends lateral resolution down to the nanometer-scale, a space region that is being now considered much closer to the probable size of segregated domains in real cell membranes. The major caveat of the surface scanning topography techniques is the previous requirement of transferring the membranes to be studied onto solid supports, and much of the description of the data available using these techniques is also devoted to showing how much the membrane–support interactions is influencing the observations. Thus, the development of new supports with the potential to capture and preserve most of the structural and dynamic features of biomembranes is a major area of development in this field. The review by Gotsu et al., for instance, analyzes in detail the utility of novel gel-like supports made of porous materials, as a corrugated surface where important features such as membrane curvature could also be studied. On the other hand, two-dimensional and three-dimensional aspects of the structure of supported membranes can be hardly understood without the proper analysis of differences in lipid and protein composition in the segregated membrane regions. This remains as a major challenge in scanning force microscopies, where the richness of the information provided by a myriad of fluorescently labelled probes is not available. The review by Saleem and Galla illustrates how the lateral organization of lipids and proteins in membranes is starting to be analyzed at the sub-micrometer scale, from the compositional point of view, with the application of time-of-flight secondary ion mass spectrometry (TOF-SIMS).

Application of surface approaches to the study of supported membranes has opened new ways to evaluate functionally important properties that were hardly accessible before. A review by Garcia-Manyes and Sanz revises recent studies on membrane mechano-chemical properties, as probed by scanning force spectroscopy. This approach allows a detailed characterization of the effect of factors like temperature, the ionic environment or the lipid composition on the mechanical resistance of membranes to rupture, at nanometer/nanonewton scales. These force profiles are being interpreted in terms of the lipid/lipid and lipid/solvent interactions that are inherent to membrane self-organization. Surface scanning microscopy of supported membranes has been also used as a versatile tool to monitorize dynamic processes in membranes, such as those occurring upon interaction of proteins, detergents, drugs or nanoparticles, as described in the article by El Kirat et al. In the same direction, a review by Garcia-Saez and Schwille illustrates how the combined application of different surface techniques has particularly benefited our

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comprehension of the correlation of membrane structure and dynamics.

In spite of all these developments, the extrapolation of the studies on supported membranes to the behavior of membranes in more relevant cellular contexts has to be made with caution. Apart from the spurious factors defined by the interaction of the membranes with the support, supported membranes neglect the contribution of relevant cellular elements, such as the membrane–cytoskeleton interactions or the dynamic processes involved in membrane homeostasis, as occurring in living cells. However, major developments in the past few years have allowed direct application of surface analytical tools to membranes in whole cells, which are assessing how different membrane properties are in a truly functional context. In this line, a review by van Zanten et al. describes the use of far-field and, specially, near-field optical microscopy (NSOM) to the study of compartmentalization in biomembranes, both from structural and dynamic points of view.

A well-established membrane-related line of research which has been successful for many years due to the application of the basic principles of surface chemistry, has been the study of phospholipid-based interfacial films prepared as models of biomembranes. The precise positioning of oriented lipid and lipid–protein monomolecular films prepared at air–liquid interfaces facilitated the application of different surface techniques much earlier than those focused on supported membranes. Two articles in this issue are devoted to surface applications on interfacial membrane-like films. The review by Mendelsohn et al. describes the use of infrared reflection–absorption spectroscopy (IRRAS) to the study of structure, molecular orientation and lipid–protein interactions in different membrane models. Zasadzinski et al., on the other hand, have elaborated a detailed model to interpret inactivation of lipoproteic pulmonary surfactant films in terms of competitive surface adsorption, a topic with biomedical relevance. As a matter of fact, the study of the pulmonary surfactant complex constitutes in itself a good example on how the understanding of the molecular mechanisms of a biologically relevant system can benefit from the application of surface chemistry approaches.

A final aspect approached in this issue is the use of supported membranes and membrane surface characterization in the development of new biotechnological applications. Two articles in this issue offer only two examples of the many recent developments that take advantage of the self-assembling properties of lipids and membranes to prepare micro- and nano-patterned surfaces useful, for instance, to design and optimize high-throughput biosensors. Fredrik Hook's group has produced in the past few years different membrane-based devices integrating nucleic acids as specific probes that could be accurately positioned in supported membrane patches. The paper by Michanek et al. gives further insight into the characterization of DNA and RNA interactions with different free-standing and supported membranes, and provides data that can permit further optimization of hybrid biotechnological devices. In the same line, the review by Oliver and Parikh describes different approaches to use patterned surfaces to prepare model membrane platforms useful for basic biophysical studies and bioanalytical devices.

I sincerely thank all the authors for their efforts to produce the solid contributions included in this issue, which I am persuaded will provide a useful and integrated view of the exciting perspectives that novel approaches and methodological developments are opening on the study and application of biomembrane systems.

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Jesús Pérez-Gil is currently Professor of Biochemistry and Molecular Biology at Universidad Complutense in Madrid (Spain). After getting his Ph. D. on Biochemistry by Universidad Complutense, he made post-doctoral stays at the Memorial University of Newfoundland in St. John's (Canada) and at the Max-Planck-Institut für Biophysikalische Chemie in Göttingen (Germany), where he approached the study of organization and lipid-protein interactions in models of the pulmonary surfactant system. Research in the laboratory of Prof. Pérez-Gil in Madrid has been focused during the last 20 years in the study of the assembly of pulmonary surfactant lipid/protein complexes, the interactions and molecular mechanisms of hydrophobic surfactant proteins and their role in optimizing respiratory biophysics. A main part of Prof. Pérez-Gil's research has required application and development of surface chemistry methodologies such as epifluorescence and atomic force microscopies or far-UV and infrared spectroscopies, on membranes, interfacial films and supported lipid and lipid-protein layers.