The Biological Membrane Structure Paradigm: One View of Its Current Condition

Thomas E. Thompson

Abstract

The biological membrane structure paradigm is alive and well, however many details, most of which are pecular to specific membranes or membrane-localized systems, need to be worked out at the molecular level.

Thomas E. Thompson
Department of Biochemistry
University of Virginia
Charlottesville, VA 22908, USA
e-mail: tet@avery.med.virginia.edu

Biol. Skr. Dan. Vid. Selsk. 1998, **49**:55–57

It has been known for many years that biological membranes separate the cell from its environment and compartmentalize the cell interior. The various membranes playing these vital roles are comprised of roughly equal weight percent protein and lipid, with carbohydrates constituting less than 10% in the plasma and nuclear membranes. Although there are many hundreds of molecular species present in any one membrane, the general organization of the generic components was established in the 1960's (Korn, 1969; Henn and Thompson, 1969). In this model, the lipids, all of which have their polar and nonpolar portions geographically segregated within each molecule, are arranged in a continuous bimolecular leaflet with the polar portions of the constituent molecules forming the two bilayer faces, and the nonpolar portions, the interior of the bilayer. This structure forms the permeability barrier for the essential, water soluble molecules and ions of the cell, and in so doing provides the basis of the compartmentalizing function of biological membranes. The protein components are of two kinds. Some are inserted into the bilayer and most traverse this structure. These so-called integral membrane proteins have amino acids with nonpolar side chains at the interface between the protein and the nonpolar central region of the lipid bilayer. Other proteins associated with the polar surfaces of the bilayer and with the intrinsic membrane proteins are termed peripheral. The carbohydrate component of those membranes that display it is covalently linked to either lipids or proteins.

The protein components confer on biological

membranes their physiological functions, which are particular for each type of membrane. The lipid component, apart from its critical barrier function, is, for the most part, physiologically silent, although derivatives of certain membrane lipids can serve as intracellular messengers. The most remarkable feature of this general structure is the fact that neither the lipid nor the protein components are covalently linked to one another or to each other. This structure formed by molecular associations only, is less than 100 Å in thickness, but many orders of magnitude larger in the other two orthogonal dimensions. Although it is mechanically surprisingly strong, it is fluid-like and as a dielectric can withstand field strengths up to 10^5 volts cm^{-2} without breakdown. Experimental and theoretical studies carried out over a period of many years have established the fact that these unusual properties are conferred on biological membranes by the lipid bilayer matrix (Henn and Thompson, 1969).

An important modification to this model of biological membrane structure was made in the early 1970's by Singer and Nicolson, who offered strong evidence that the molecules, both lipid and intrinsic proteins, comprising this structure undergo a variety of thermally-driven motions (Singer and Nicolson, 1972). Both types of molecules diffuse laterally, and rotate about an axis normal to the membrane plane. In addition, the lipids can flip from one face of the membrane bilayer to the other and adsorb/desorb from the bilayer at slow, but measurable rates. Although these latter motions are forbidden to intrinsic proteins, both lipids and proteins can to some degree exhibit limited bobbing motions normal to the membrane plane. As a corollary to this idea of a dynamic membrane structure, which came to be known as the fluid mosaic model, the notion rapidly developed that within the planar confines of the membrane, the molecular components formed a two-dimensional, anisotropic, stochastic system.

In recent years, the random character of the in-plane mix of the membrane molecules has given way to the realization that, although the dynamic aspect is correct, there is considerable order in the plane of the membrane. This order takes the form of a compositional mosaic of molecular association complexes in the membrane plane (Jacobson and Vaz, 1992). The plane of the biological membrane is thus compartmentalized by domain structures much as the three dimensional space of the cell is compartmentalized by the membranes themselves. The dimensional range of the domain mosaic runs from tens of microns to tens of nanometers over persistence intervals of minutes to nanoseconds. Because of these large ranges in time and space, experimental investigation of domain structure is limited by the spatial and dynamic ranges intrinsic to a particular method. This fact has given rise to much confusion and apparently conflicting information about membrane domain structure.

In addition to this in-plane domain structure, it has been known for some time that the two lipid monolayers comprising the membrane bilayer do not in many membranes have the same composition. This transbilayer lipid compositional asymmetry appears to be in large part stable in the absence of metabolic energy. Whether the stability is an equilibrium or a kinetically-trapped configuration is not known (Devaux, 1991). This lipid asymmetry and the fact that intrinsic membrane proteins do not rotate about an axis in the membrane plane, combine to make the two faces of the bilayer separate domains.

The membrane paradigm outlined above incorporates the features that are at present known to be common to most, if not all, biological membranes. Many questions remain unanswered, however. A large number are specific to individual membranes and their idiosyncratic functions. Some questions are more general. Important among these are the physical basis or bases of in-plane domain structure and its physiological consequences. The ultimate physical basis for domains in membranes must, of course, lie in the interactions between molecules. Interactions can not only give rise to association complexes of molecules that specifically interact with each other, but also to groups of molecules that do not specifically interact but are excluded from other association complexes and thus form domains by default. Interactions that are important in forming domain structures can occur between membrane proteins, or

between these molecules and proteins of the cytoskeleton and cytoplasm. Association domains can equally well be the result of interactions between membrane proteins and lipids or between different types of bilayer lipids. Obviously, in any membrane at any time these interactions can operate singly or in combination. The non-ideal mixing that is characteristic of membrane lipids can be used to understand domain structure arising from the coexistence of multiple lipid phases. The basis of domain structure formed by membrane proteins is more varied and is dependent on highly specific interactions between molecules. A unitary hypothesis applicable to all such protein-protein association complexes is probably impossible to formulate. Interactions between membrane proteins and lipids of the bilayer are more fully understood (Mouritsen and Bloom, 1993; Mouritsen et al., 1996).

We have suggested that modulation by the cell of the percolation properties of its membrane domain systems can be used to control the extent and rate of physiologically important in-plane molecular interactions (Thompson et al., 1992). This idea has been examined experimentally using simple two-component, two-phase phospholipid bilayers in which interactant molecules are confined to the fluid domains in temperature and composition ranges where both solid and fluid lipid phases co-exist. The results of the experimental studies agree well with computer simulations of such systems (Sankaram et al., 1992; Piknova et al., 1996; Schram et al., 1996; Schram and Thompson, 1997; Piknova et al., 1997). Taken together, this work provides strong support for the idea that domain structures in the plane of bilayer membranes can have a marked effect on the apparent equilibrium poise and effective rates of in-plane reactions. Although this work has been carried out on two-component lipid bilayers and utilizes the coexistence of solid and fluid domains as the interaction domain matrix, the conclusions drawn are applicable to any planar domain system regardless of its physical origin.

References

Devaux, P.F. 1991. Static and dynamic lipid asymmetry in cell membranes. *Biochemistry* 30:1163-1173.

Henn F.A., and T.E. Thompson. 1969. Synthetic lipid bilayer membranes. *Ann. Rev. Biochem.* 38:241-262.

Jacobson, K., and W.L.C. Vaz (eds). 1992. *Comments on Molecular and Cellular Biophysics.* 1992. 8:1-114.

Korn, E.D. 1969. Cell membranes: structure and synthesis. *Ann. Rev. Biochem.* 38:263-288.

Mouritsen, O.G., and M. Bloom. 1993. Models of lipid-protein interactions in membranes. *Ann. Rev. Biophys. Biomol. Struct.* 22:145-171.

Mouritsen, O.G., M.M. Sperotto, J. Risbo, Z. Zhang, and M.J. Zuckermann. 1996. Computational approach to lipid-protein interactions in membranes. *Adv. Comp. Biol.* 2:15-64.

Piknova, B., D. Marsh, and T.E. Thompson. 1996. Fluorescence quenching study of percolation and compartmentalization in two-phase lipid bilayers. *Biophys. J.* 71:892-897.

Piknova, B., D. Marsh, and T.E. Thompson. 1997. Fluorescence quenching and ESR study of percolation in a two-phase lipid bilayer containing bacteriorhodopsin. *Biophys. J.* 72:2660-2668.

Sankaram, M.B., D. Marsh, and T.E. Thompson. 1992. Determination of fluid and gel domain sizes in two-phase lipid bilayers: an ESR spin label study. *Biophys. J.* 63:340-349.

Schram, V., H-N Lin, and T.E. Thompson. 1996. Topology of gel-phase domains and lipid mixing properties in phase-separated, two-component phosphatidylcholine bilayers. *Biophys. J.* 71:1811-1822.

Schram, V., and T.E. Thompson. 1997. Influence of the intrinsic membrane protein bacteriorhodopsin on the gel phase domain topology in two-component phase separated bilayers. *Biophys. J.* 72:2217-2225.

Singer, S.J., and G.L. Nicolson. 1972. The fluid mosaic model of the structure of cell membranes. *Science* 175:720-731.

Thompson, T.E., M.B. Sankaram, and R.L. Biltonen. 1992. *Comments on Molecular and Cellular Biophysics* 8:1-15.