Course : PG-Pathshala
Paper-12 : Membrane Biophysics
Module 02 : VARIOUS MEMBRANE MODELS INCLUDING FLUID-MOSAIC MODEL
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Learning objectives: The membrane is fundamental structural unit for cellular organization and various biological functions of cell are dependent upon the membrane structural integrity. Therefore, it is at-most important to study the structure of membrane. However, the structure of membrane was elucidated by different researchers as different cell membrane models until a well accepted 'fluid-mosaic model' of cell membrane was proposed. Present module elucidated various cell membrane models and fluid-mosaic model in detail.

Introduction: Membrane Models (Historical perspective)

Cell membrane as the name suggests is the outermost covering of the cell separating the inner cellular protoplasm from its external environment. The word 'cell membrane' was coined by C. Nageli and C. Cramer In 1855. The essentiality of cell membrane may be proved by the fact that about a 33% of the dry weight of a cell is made-up of its membrane and more than 40% of all proteins encoded by a eukaryotic genome are present at membrane as membrane proteins. Thus a large number of biological processes occur with the help of cell membranes. Among these major roles are controlling the chemical traffic into and out of the cell, anchoring the cytoskeleton to provide shape to the cell and cell signalling. The semi-permeable nature of the membranes allows selective movement of the substances across the cell which is very important for its survival. The most important function of these bio membranes is to protect the cell from its external environment.

Today, we know that chemically cell membranes are made up of lipids (20- 40%), proteins (60-75%) and carbohydrates (1-5%), but a whole lot of study have undergone to decipher the structure of the cell membrane. Various models have been proposed to elucidate the structure of membranes. These models have been proposed based on the extensive research carried out by different scientists enabling them to elucidate the structure of the membranes. The present-day perception of cell membrane is entirely based on the understanding of these past membrane models.

OVERTON CONCEPT OF LIPID STRUCTURES OF MEMBRANE

Charles Ernest Overton played a very important role in the understanding of the picture of cell membranes. He studied the permeability of the cell membrane to a wide variety of substances, nearly 500 different plant and animal cell models. He noticed that substances that are non-polar in nature (ether soluble) did not result in the shrinking of cells, contrary to water soluble (polar) substances, irrespective of their molecular size. He reached to the conclusions what we know as the Overton's rules according to which the substances that are soluble in oil enter the living cells faster whereas substances that are highly soluble in water enter the cell slowly. Further, he proposed "Lipoidal theory" in 1899 according to which all living cells are covered by a thin layer of lipoid materials. He suggested that cholesterol and phospholipids could be the main components of cell membranes. Initial predictions related to lipid content as a major ingredient were justifiable, however, this model of cell membrane had several demerits e. g. there was no explanation for the movement of water and other hydrophilic substances across the cell boundaries and no idea related to energy dependent selective transport system.

IRVING LANGMUIR MODEL: Structural elucidation of cell membrane through artificial membranes

Attempts to build artificial membranes provided insight into the structure of real membranes and this elucidation came into the picture when Irving Langmuir (in 1917) discovered that phospholipids dissolved in benzene would form a film on water after the benzene evaporation from system. He carefully measured surface area occupied by known quantities of oil using specially designed apparatus called as Langmuir trough. This apparatus was originally designed by Agnes Pockels in which mono layers of lipids were spread at the air-water interface. The hydrophilic heads were immersed in water whereas the hydrophobic hydrocarbons arepointed toward the air phase (Fig.1). Langmuir was later received Nobel Prize in chemistry in 1932 for his work in surface chemistry.

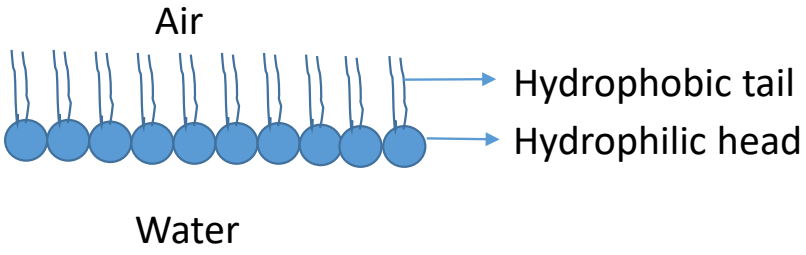


Figure1: Artificial lipid monolayer orientation at the air-water interface. The hydrophilic phospholipids are oriented towards water and hydrophobic tails are excluded towards air.

GORTER AND GRENDEL CELL MEMBRANE MODEL (1925)

Gorter and Grendel were the first to propose that the lipids of the cell membrane are organised in a bimolecular lipid sheet. They experimentally calculated the surface area of lipids isolated from red blood cells from various animals like sheep, rabbit, goat and human in acetone. The red blood cells were chosen since these cells were known to lack internal membranes, they assumed that all lipids should come from the cell envelopes. Using Langmuir trough the lipids were spread on a water surface and the area was measured. They also measured the surface area of the red blood cells from the microscopic images. On comparing the surface area of the lipid to that of the red blood cells they found that surface area of the lipid was exactly twice to that of the red blood cell. They concluded that lipids of the cell membrane are organised in a bimolecular lipid sheet. They proposed the structure such that two lipid layers form a bilayer with the polar head (hydrophilic) groups pointing toward the aqueous exterior environment and non-polar (hydrophobic) ends of the lipids embedded in the centre (Fig.2). This model was named as 'bimolecular lipid leaflet model'.

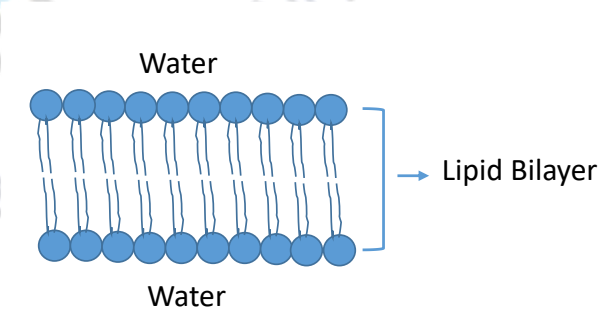


Figure2: Lipid bilayer structure as proposed by Gorter and Grendel. The hydrophilic heads pointing toward the aqueous environment and hydrophobic ends of the lipids embedded in the centre.

Although the attempt for describing the structure of membrane and lipid bilayer concept was correct, however, there were some limitations were seen later in this model. The extraction technique used for lipid isolation could not extract erythrocyte lipids from the samples completely. Several mis-calculations happened in measuring the total area of the red blood cells and also this model unable to describe various crucial functions of the cell membrane.

SANDWICH MODEL OF CELL MEMBRANE BY DANIELLI AND DAVSON

The ‘sandwich model’ or the ‘lamellar model’ of cell membrane as proposed by Jim Danielli and Hugh Davson (1935) relates the structure of the membrane to its chemical properties. After the Gorter and Grendel work on the bilayer structure of the lipids Harvey and Coley (1931) and Danielli and Harvey (1935) did an extensive study to study the surface tension of the cell membrane. They observe that the cell membrane showed lower surface tension compared to bimolecular lipid leaflet. Based on their observation they pointed out the presence of protein molecules adsorbed on the surface of lipid droplets which reduce the surface tension of droplets.

In 1935 Jim Danielli and Hugh Davson proposed that biological membranes are made up of lipid bi-layers that are coated on both sides with absolute layer of protein (lipid bilayer sandwiched between two layers of protein). The hydrophilic polar heads of the lipid molecules are directed towards the proteins (Fig. 3). The close association between the two is maintained by electrostatic forces. The hydrophobic non-polar tails of the two lipid layers are embedded in the centre where they are held together by hydrophobic bonds and van der Waals forces. The model assumed the cell membrane to be a stable structure with very little variability and functional specificity.

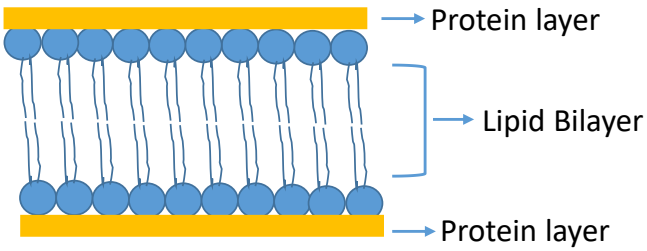


Figure 3: Diagrammatic representation of sandwich model proposed by Danielli and Davson

In early 1950s Danielli and Davson made several modifications for the sandwich model to explain the physiological function of the cell membranes. They suggested that glycoproteins might be adsorbed to the outer membrane surface, thereby accounting for the antigenic properties of cell membranes. They also speculated the presence of certain (bridges) between the outer and inner protein layers through which certain materials are ex-changed between a cell and its environment.

The Danielli Davson's model also had several demerits due to which it was later on got modified by other researchers. This model showed that all the membranes have a constant lipid-protein ratio with uniform thickness and therefore, have symmetrical internal and external surfaces. The model could not explain the permeability of certain substances through the membrane.

ROBERTSON UNIT MEMBRANE MODEL

So far all the cell membrane structures predicted were based on indirect studies. It was for the first time that Robertson proposed in 1959 his famous unit membrane model based on the experimental evidences from electron microscopy. The membranes were fixed with osmium tetra-oxide and potassium permanganate ($KMnO_4$) which revealed a characteristic tri-laminar structure of the cell membrane consisting of two parallel outer dark (osmiophilic) layers and a central light (osmiophobic) layer (Fig. 4).

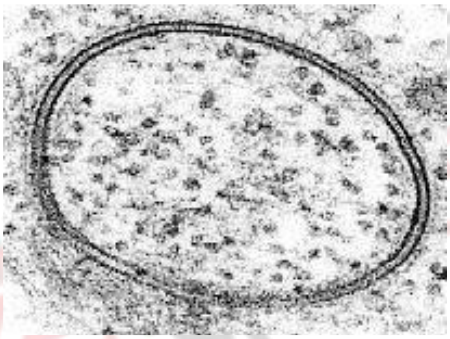
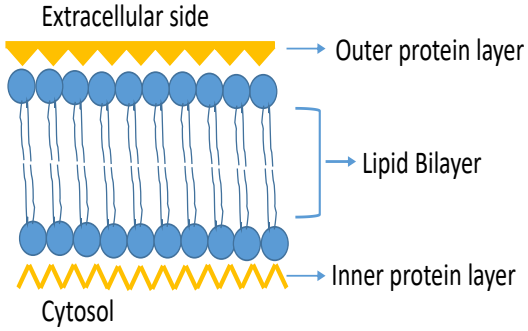


Figure4: Electron micrograph showing the trilaminar nature of cell membrane consisting of two parallel outer dark (osmiophilic) layers and a central light (osmiophobic) layer.
Source:http://upload.wikimedia.org/wikipedia/commons/7/7b/Annular_Gap_Junction_Vesicle.jpg

The thickness of osmiophilic layers measured was 2.0-2.5nm and that of the osmiophobic layers measured was 2.5-3.5 nm. The total thickness of the trilaminar structure measured 6.5-8.5 nm. This value when compared with the thickness predicted on the basis of chemical studies was same. The tri-laminar structure (dark-light-dark) was presumed to be universal for all cell membranes including the endoplasmic reticulum, hence the name unit membrane model.

Robertson proposed that the unit membrane structure consisted of a bimolecular lipid leaflet sandwiched between outer and inner layers of dense protein (Fig. 5). He also proposed that all bio membranes are either made of a unit membrane or a multiple of unit membrane. In

unit membrane layers are outer surface muco- on the inner surface protein.



model the protein asymmetrical i.e. on the protein is present while it is non-mucoid

Figure 5. : Diagrammatic representation of Robertson Unit membrane model

Robertson model was basically the confirmation of earlier two models i.e. Gorter & Grendel (1925) model and Danielli Davson (1935) sandwich model. However, Robertson's model was sometimes incorrectly interpreted as that all membranes have the same composition. Cell membrane, membranes of endoplasmic reticulum, golgi complex and lysosomes are unit membranes while nuclear membrane, membranes of mitochondria and plastids are double unit membranes. However, Robertson's statement was merely meant to describe a common structure.

FLUID-MOSAIC MODEL OF CELL MEMBRANE

S.J. Singer and G. Nicholson in 1972 presented the most widely accepted model till date the 'fluid mosaic model' which is the culmination of all the membranes models predicted earlier. According to the fluid mosaic model membranes are two-dimensional solutions of oriented lipids and globular proteins. The concept of lipid bilayer remains as such as predicted in earlier studies however the presence of protein as continuous sheath on either surface of lipids was reformed. In this mosaic model the proteins are present both on the surface of the lipid membrane as well as found embedded in the lipid bilayer or span through the membrane. The proteins present on the surface are more hydrophilic in nature and are called as the Peripheral proteins, non-covalently linked to the polar heads of phospholipids molecules (Fig.6). Peripheral proteins are loosely attached to the membrane surface and can easily be separated from the membrane by mild treatment.

The proteins found embedded in the matrix are called as the Integral proteins. They are hydrophobic in nature having affinity for the hydrophobic tails of phospholipids on interior of the layer. Integral proteins form the major fraction of membrane proteins nearly 70% of the total protein and cannot easily be separated from the lipids as compared to the peripheral

proteins. Several integral proteins form a tunnel like passage which allows for the movement of water and water soluble substances.

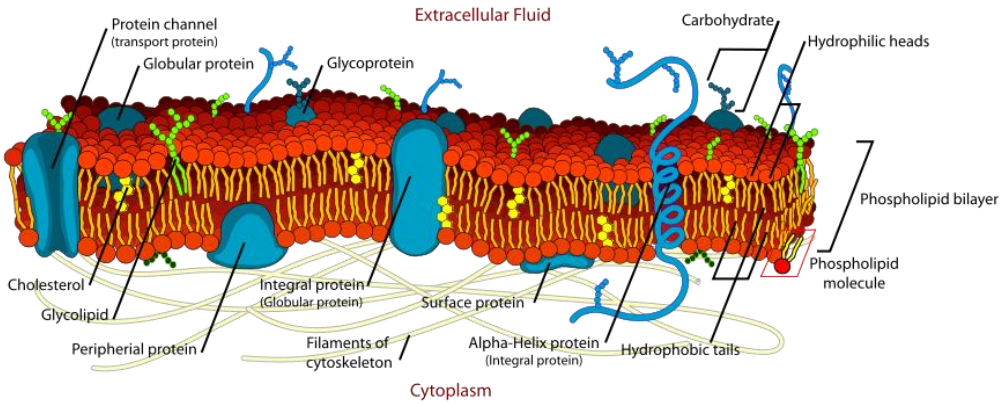


Figure6: Fluid-mosaic model of cell membrane. Source:https://en.wikibooks.org/wiki/Alevel_Biology/Biology_Foundation/cell_membranes_and_transport

The lipid bilayer has two important role one it acts as a solvent for integral membrane proteins and second it acts as a permeability barrier. Membrane lipids and proteins are free to diffuse laterally provide flexibility and dynamism to the membrane.

The fluid mosaic model of cell membrane is still the widely accepted model. In particular, due to advancement in the visualization and confirmation of membrane proteins it is nowadays known that membrane proteins display α-helical and β-barrel confirmations in the membrane spanning domains.

Summary:

Various models of cell membrane with researchers are given as the tabulated form (table 1) in ascending order of time gaps.

Table1: Landmarks discoveries in the history of membrane models.

Year	Scientists	Contribution

1895	Charles Ernest Overton	Postulated "**Lipoidal Theory"** according to which all cellmembranes are 'impregnated' by lipid like material. Compounds soluble in organic solvents entered the cell more rapidly than water-soluble compounds
1917	Irving Langmuir	Developed an apparatus called as "**Langmuir Trough**". With this apparatus area occupied by monolayer films could be measured
1925	Gorter and Grendel	The structure of the membrane is bilayers, two molecules thick. Lipids of the cell membrane are organised in a **bimolecular lipid sheet** with hydrophilic heads pointing toward the aqueous environment and hydrophobic ends of the lipids embedded in the centre
1935	Danielli and Davson	They proposed the famous **Sandwich Model**. According to which bilayer lipid is sandwiched between two layers of protein
1950	J.D. Robertson	Proposed the **Unit Membrane model** which revealed the typical trilaminar appearance of the membrane consisting of two parallel outer dark (osmophilic) layers and a central light (osmophobic) layer
1972	S.J. Singer and G. Nicholson	Presented the most widely accepted model the **Fluid Mosaic model**. The membrane is a fluid structure in which a mosaic of different types of proteins are embedded