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## Lipids, membranes and beyond

Cells are separated from their neighbours and environment by lipid membranes only 5–10 nanometres thick. Biophysicist Darius Köster explores recent research that has extended our understanding of membrane structure and function

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Biological molecules

Carbohydrates, lipids and proteins

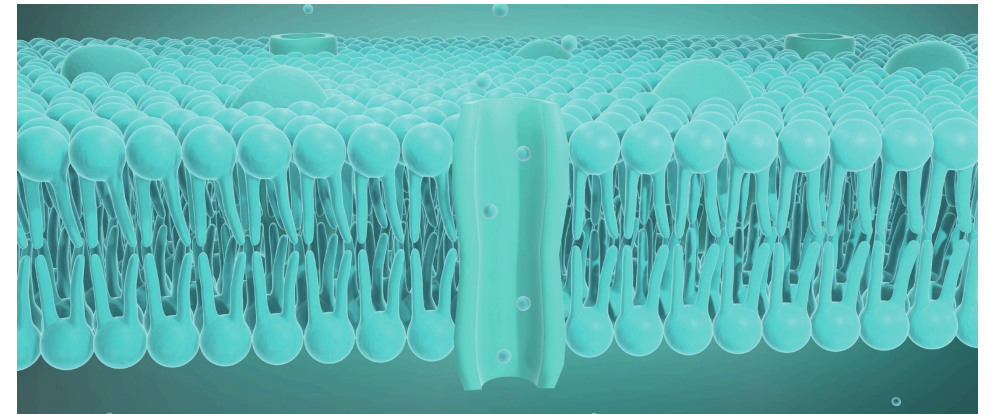
Cell membranes

Cells

Disease and the immune system

Studying cells

Darius Köster



### EXAM LINKS

**AQA** Lipids; Methods of studying cells; Transport across cell membranes

**OCR A** Triglycerides and phospholipids; Biological membranes

**OCR B** Plasma membranes

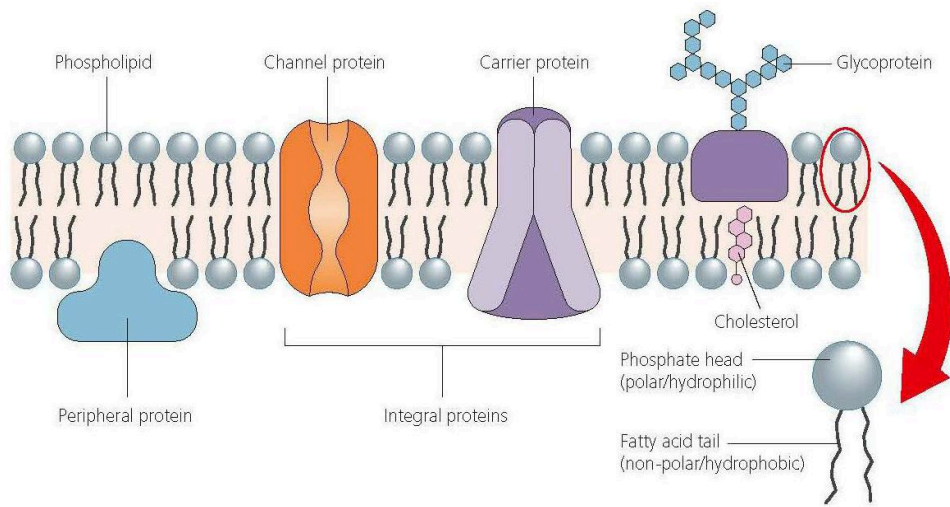
**Pearson Edexcel A** Lipids; Structure and properties of cell membranes

**Pearson Edexcel B** Lipids; Cell transport mechanisms

**WJEC Eduqas** Lipids; Cell membranes and transport

The fluid-mosaic model of cell membranes (see Figure 1) holds that the fluid-like environment of the phospholipids includes proteins and glycolipids that form a mobile mosaic within the bilayer. The model suggests that there are no restrictions to lateral movements of the lipids and other components, and that there is a range of molecules and signals that cross the membrane. The model was first described in the 1970s, but scientists have continued to discover more about the composition, flexibility and functions of membranes.





**Figure 1 Fluid-mosaic model of a cell membrane**

## Evolution of membranes

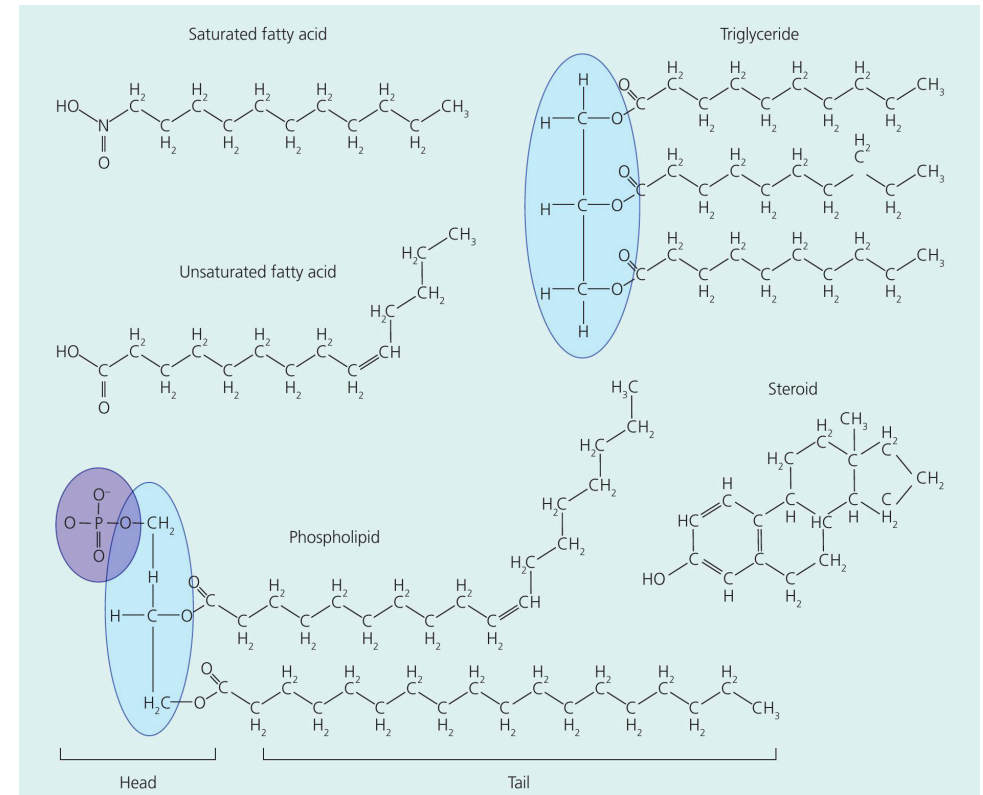
Recent estimates for the age of the last universal common ancestor of life extend to around 4 billion years ago. An early evolutionary event required biochemical material to be separated from its environment by a barrier – perhaps within a vesicle.

Current ideas about how membranes first formed come from studying biochemical events in thermal vents, hot ponds and laboratories. These suggest that the first membranes were formed from molecules that had both hydrophilic and hydrophobic parts. The first vesicles might have been made of proteins, but lipids are the membrane molecules in all present-day life forms. Therefore, while we accept that in existing organisms all cells arise from other cells, at some point in our evolution membranes evolved and this represented a momentous event.

Lipid membranes allow the encapsulation of genetic material and other components, without losing them to the outside. In eukaryotic cells lipid membranes not only separate a cell from its environment but also form intracellular compartments.

## Structure of lipids

Lipids exist in several varieties, including triglycerides, phospholipids and steroids (see Figure 2).



**Figure 2 Chemical structure of fatty acids and lipids. The glycerol moiety is shown in blue in both the triglyceride and phospholipid**

Lipids and fatty acids are classified as unsaturated if they contain a double carbon bond. Fatty acids are important in providing energy and essential fatty acids that our cells cannot synthesise, such as omega-3 and omega-6. These are named from counting the carbons from the methyl tail before the first double bond. These unsaturated fats need to be obtained from food (see Box 1).

Structurally saturated fatty acids have no open carbon bonds and are considered unhealthy because they stop the liver breaking down cholesterol. Mono- and poly-

unsaturated fatty acids are considered to be healthier. There is evidence that certain unsaturated fats alter the way the liver processes fats from the diet, resulting in a lowering of cholesterol held in **low-density lipoproteins** (LDLs).

### Box 1 Lipids in our food

Many of our foods contain lipids – for example, butter, whole milk, meat, nuts, avocados and fried food. This part of our diet plays an important role in our body's ability to generate the variety of lipids necessary for our membranes, metabolism and energy storage. Mono- and poly-unsaturated fats are commonly obtained from plant sources, such as walnuts and flaxseeds, and from animals such as oily fish. Trans fats are rare in nature and almost all come from processed foods.



**Unsaturated fat sources**



**Trans fat sources**

### Membrane consequences

Being **non-polar molecules**, lipids are soluble only in non-polar solvents, such as ethanol or chloroform, and not water. Membrane phospholipids are amphipathic – these are molecules with both hydrophilic and hydrophobic parts. Their polar head can be surrounded by water molecules, while the lipid tail lacks water solubility. This results in them moving away from polar solvents. The amphipathic property of phospholipids is the reason they spontaneously form membranes when they are in an aqueous environment, minimising hydrophilic interactions. Multiple lipids self-organise in a double row, with the hydrophobic tails facing each other and the hydrophilic heads facing the water.

Self-organised membranes have very interesting and unique properties. The lipids within one of the two layers can move freely within that layer because there are no chemical bonds between the lipids. Lipid membranes are flexible and can take on many different shapes, but they can only be stretched a little and rupture easily.

This is a consequence of physical properties known as **stretching modulus** and **bending modulus**. With the low resistance of lipids to stretching forces, the tension

in animal cell membranes is largely provided by the interaction of the membranes with the cells' cytoskeletons, particularly with actin filaments.

## Movement in membranes

Since all phospholipids are amphipathic, a membrane can be a mixture of these molecules – indeed, the two layers of a membrane can consist of different lipids. This is what happens in cells. For a long time we knew that the cell membrane contains different types of lipid. Recent technical advances have revealed that hundreds of types of lipid form each layer of the cell membrane. To make things more complicated the cell also makes a lot of proteins that either insert into the membrane or bind to it (see Figure 1).

In a cellular lipid membrane, it is the membrane proteins that fulfil the important role of allowing specific ions or molecules in and out. Channel proteins enable facilitated diffusion, while carrier proteins require active transport mechanisms. Membrane-spanning receptor proteins enable signals to pass through when the right ligand binds to them. Proteins also allow molecular sensing and transduction of temperature and of mechanical force.

## Updating membrane models

The fluid-mosaic model suggests that lipid membranes have a passive role in providing a platform for embedded signalling proteins, and that they can move freely. But this picture has changed as our understanding of how the specific local lipids are arranged to play a role in ensuring the correct function of signalling proteins.

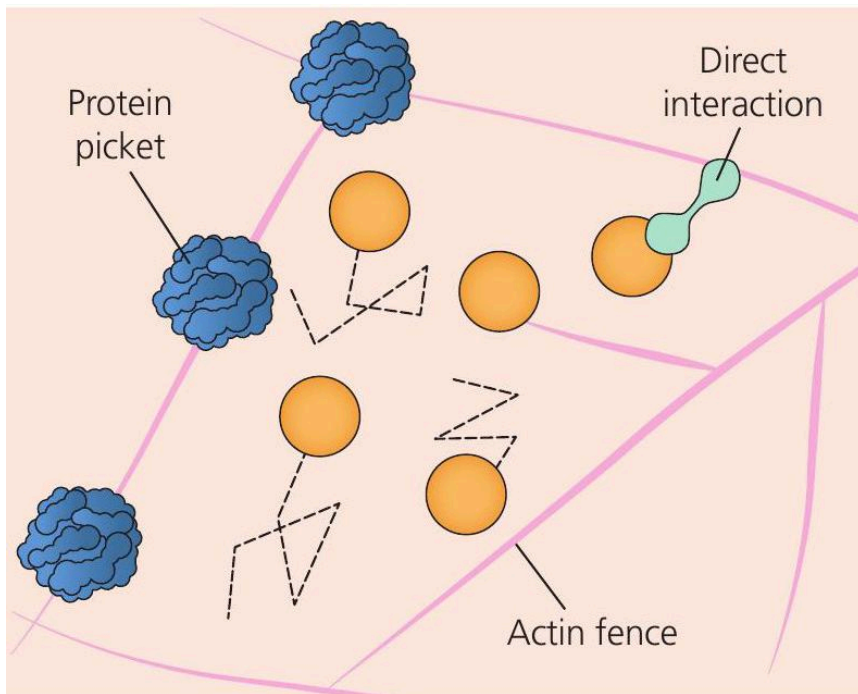
One important tool that scientists use to study lipid membranes in living cells is fluorescence microscopy. This is a powerful technique in biology in which proteins and lipids of choice are marked with small fluorescent molecules called fluorophores. Fluorophores emit light after having been activated with a laser to excite them at a specific wavelength. This reveals the position of the label in the cell. While individual proteins have been tracked, the optical resolution of fluorescence microscopes is not sufficient to follow individual lipids. However, information about the dynamics

of single lipids, or how closely packed they are along the cell membrane, can be inferred.

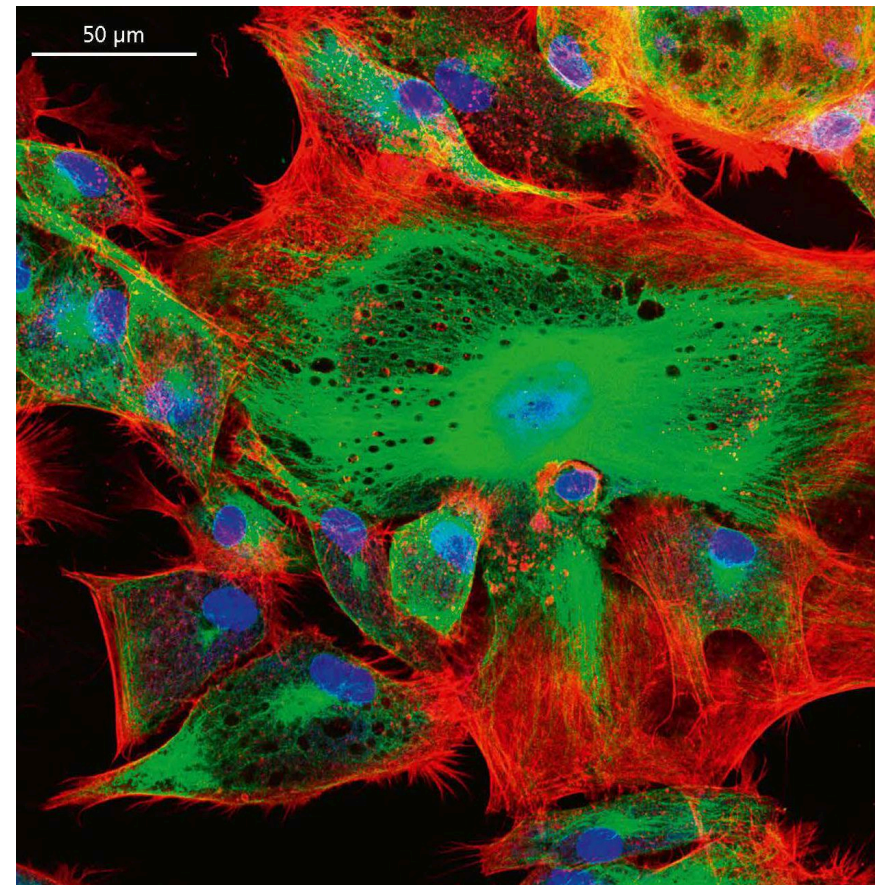
In 2005 the Japanese scientist Kusumi and colleagues observed that many types of lipid did not move freely and laterally across the cell membrane as people had assumed. Instead they were confined in a small area, before again travelling a bit further and again stalling. When the researchers analysed many such lipid tracks, they found that the size of the small entrapment areas was the same for all experiments on the same type of cell, but was different when they used a different cell type. The idea of lipid-rafts that held specific proteins and controlled specific signalling events emerged. It turned out that the entrapment area was set by the underlying network of actin filaments that make up the cell cortex (see Box 2).

### Box 2 Picket fence model

The cell cortex is part of the cytoskeleton that gives eukaryotic cells their shape and mechanical stability. The main components of the cell cortex are actin filaments and molecular motors, such as myosin. Figure 2.1 shows the picket fence model of the cell membrane, where a lattice of actin filaments underlying the membrane generates a fence for membrane proteins, and membrane proteins binding directly to actin act as pickets, hindering the motion of other lipid molecules.



**Figure 2.1** Inner view of a cell membrane showing the association of actin with specific proteins. Orange circles represent lipids tracked and confined within an area

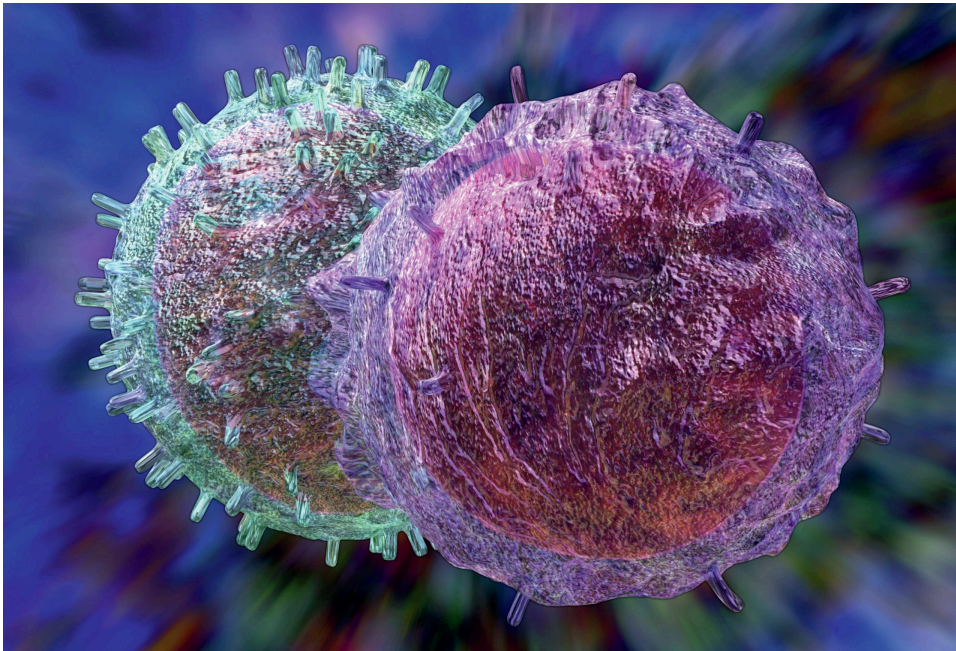


**Fluorescence micrograph of human fibroblasts in culture. The actin cortex, lying under the cell membrane, is labelled in red. The microtubules are green and the nuclei blue**

Recent work has shown that active movement of actin filaments by molecular motors can cause lipids or membrane proteins to form the temporary clusters that are necessary for signalling.

Most membrane research uses individual cells in a culture dish (see Box 2) or cells within a simple organism such as the fruit fly (*Drosophila melanogaster*). This allows us to study membranes in their native condition. We can alter key components of the cell by using pharmacological drugs that perturb the actin network or remove cholesterol from the membrane, or by increasing or decreasing the expression of a specific protein in the cells. But manipulations of cells are limited, and it is often

difficult to pinpoint the effect of a single protein because the cell has many ways of adjusting and compensating. One way to circumvent these issues is to recreate the system with a minimal set of components – called the watchmaker’s approach.



**A B cell (blue–green) synapsing with a T cell (purple). Actin is condensed at the immunological synapse**

We are using such approaches to gain a better understanding of the activation of T cells in our immune system. When a T cell meets an antigen–presenting cell and is activated, the T cell forms an **immunological synapse**, and a cascade of signalling and protein modification events help trigger the immune response. This activation results in specific membrane proteins forming clusters that move towards the immunological synapse. The actin cortex drives this transport using motor proteins related to myosin (see BIOLOGICAL SCIENCES REVIEW Vol. 35, No. 3, ‘The cytoskeleton’). The protein clusters in the membrane change their composition and hence how strongly they stick to actin along the path

Therefore, our current understanding is that cell membranes are tightly intertwined with the cell’s cytoskeleton, forming an active, dynamic system that is being

constantly remodelled and renewed. Many aspects of this system are still unclear, and many more discoveries will certainly follow, leading to a better understanding of this essential part of every cell.

## TERMS EXPLAINED

**Bending modulus** A measure of stiffness.

**Low-density lipoprotein** A fat carrier found in extracellular fluid, also referred to as a carrier of ‘bad cholesterol’.

**Immunological synapse** The interface between an antigen–presenting cell and a lymphocyte.

**Non-polar molecule** A molecule carrying no separation of charge.

**Stretching modulus** A measure of the relative extension of an object per unit force.

## KEY POINTS

- Membranes protect the cellular environment.
- Lipids exist in many forms.
- Some lipids are essential and only obtained from our diet.
- The movement of lipids is not entirely free across a membrane.
- The membrane interacts directly with the cell cytoskeleton.

## RESOURCES

Julius and Patapoutian’s Nobel prize–winning work on membranes:

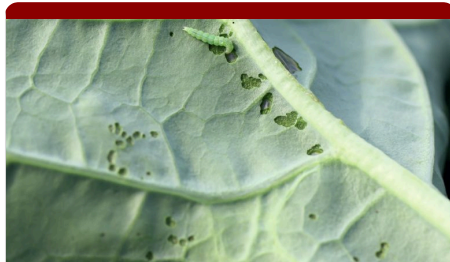
<https://tinyurl.com/Nobel-membranes>

**Darius Köster** is an assistant professor at Warwick Medical School, University of Warwick. He researches the molecular and physical principles that govern processes in cell membranes.

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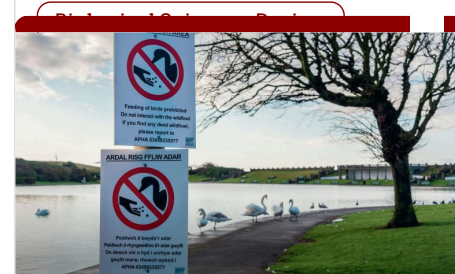
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