**Introduction**

Does cell membrane physiology degrade over time?  
Can the physiologic function of cell membranes be improved?  
If cell membrane functionality can be improved, is there clinical benefit to patients?

**Review of cell membrane structure**

The basic knowledge regarding the structure of biological membranes has been developed over a relatively extended period, starting in the 1880s and continuing through the 1960s, when Stoeckenius (1962) described why electron photo micrographs showed three apparent layers, which turned out to be the phospholipid bilayer. [http://www.nature.com/scitable/topicpage/discovering-the-lipid-bilayer-14225438, accessed 10.20.13] As it turns out, experiments showed that phospholipids could spontaneously form a bilayer when mixed with water.

![Diagram of lipid bilayer](null)

However, the membrane is a bit more complex than simply a so-called lipid bilayer. There are four principle phospholipids—phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, and sphingomyelin—which constitute 50 to 60% of total membrane lipid. The fatty acid tails attached to the phospholipid heads are critical for maintaining membrane fluidity: the interactions between short chain fatty acids are weaker than those between longer chains, so membranes containing short fatty acid chains are less rigid and remain fluid at lower temperatures. Unsaturated fatty acids also increase membrane fluidity because the presence of double bonds introduces kinks in the fatty acid chains, making them more difficult to pack together. Lipid bilayers behave as two-dimensional fluids in which individual molecules, both lipids and proteins, are free to rotate and move in lateral directions. Cholesterol is another important membrane lipid, helping to maintain both membrane rigidity near the outer margin of the membrane and fluidity at lower temperatures deeper within the membrane.
The cholesterol molecule locates mainly in the outer leaflet of the membrane. The red dot in the figure above represents the polar/hydrophilic domain of the cholesterol.

Proteins are the other major constituent of cell membranes, making up 25 to 75% of the mass of various membranes of the cell. The working model of membrane structure, proposed by Singer and Nicolson in 1972 [Singer SJ, Nicolson GL. The fluid mosaic model of the structure of cell membranes. Science. 1972 Feb 18;175(4023):720-31.] views membranes as a fluid mosaic in which proteins are inserted into a lipid bilayer; membrane proteins carry out the specific functions of the different membranes of the cell. For example, the inner mitochondrial membrane contains about 75% protein which is involved with the electron transport chain (oxidative phosphorylation and energy production via ATP).
The transmembrane proteins (comprised of channel and carrier proteins) act as transporters and determine the selective permeability of cell membranes vs. simple diffusion by simple molecules such as oxygen and carbon dioxide. It is these specific transporters that constitute membrane receptors for minerals, glucose, hormones and other biological molecules required for normal cell function and growth. For example channel proteins transport inorganic ions such as Na\(^+\), K\(^+\), Ca\(^{2+}\), and Cl\(^-\), whereas carrier proteins transport more complex molecules like glucose. In order to transport substances across the membrane, the proteins undergo conformational changes which require membrane fluidity in order to occur.


**Lipid rafts**

More recent research (since year 2000) has demonstrated non-homogeneous regions within the cell membrane termed lipid rafts. These rafts provide fluid platforms that segregate membrane components and dynamically compartmentalize membranes. These assemblies are composed mainly of sphingolipids and cholesterol in the outer
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leaflet of the membrane. A review by Lingwood and Simons stated that lipid rafts are fluctuating nanoscale assemblies of sphingolipid, cholesterol, and proteins that can be stabilized to coalesce, forming platforms that function in membrane signaling and trafficking.

This graphical representation of two lipid rafts (blue bilayer) within a cell membrane shows the typical increase in cholesterol and sphingomyelin concentrations.

Key: PC, phosphatidylcholine; PE, phosphatidylethanolamine; PS, phosphatidylserine; PI, phosphatidylinositol, SPM, sphingomyelin, Chol, cholesterol; Gang, gangliosides.

Cell membrane degradation
Phospholipid degradation
Aging causes detrimental changes in membrane phospholipid composition. Phosphatidylcholine is one of the main types of phospholipids in the cell membrane, and its concentration within the cell membrane decreases with age, whereas sphingomyelin and cholesterol both increase with age. Every cellular membrane in body is affected as well as the organelles within the cell such as the mitochondria. Phosphatidylcholine decline limits the body’s homeostatic ability by decreasing membrane fluidity. Decreased cell membrane fluidity and decomposition of cell membrane integrity, as well as break down of cell membrane repair mechanisms, are associated with various disorders, including liver disease, atherosclerosis, several cancers and ultimately cell death.

The phospholipids have a polar head group and two hydrocarbon tails. Phosphatidylcholine is the predominante head group in the outer leaflet of the membrane bi-layer. Phosphatidylcholine associates with highly unsaturated fatty acids, especially arachidonic acid. The implication is that the outer layer has higher energy lipids than inner layer of membrane.
Phosphatidylcholine’s role in the maintenance of cell-membrane integrity is important to all of the basic biological functions. These include information processes that occur within cells from DNA to RNA to proteins and the maintenance of cellular energy and intracellular communication.

Sidebar:
Three scientists have won the Nobel Prize for medicine/physiology after discovering how cells precisely transport material. James Rothman and Randy Schekman, both from the US, and Thomas Sudhof, from Germany, shared the prize. They determined the way vesicles transport substances, such as neurotransmitters or hormones, to an exact destination. Vesicles may the thought of as minute membrane-bound spheres used by the body as transport containers. Rothman found receptor proteins embedded in the vesicles which allow the vesicles to bind with a similarly coded receptor at the precise location where their contents are required. Dr Lisa Swanton, from the University of Manchester, said it well: “Vesicles are like a postman’s bag, they have to get to a specific address. They have worked out the mechanism of sending to the right location, they have advanced the field enormously.”

Fatty acid degradation
Fatty acids within the cell membrane degrade when dietary fats are either oxidized (lipid peroxides can form within the body as well) or contain trans fatty acids.
Trans fatty acids
There are two principle sources of dietary trans fatty acids. Naturally occurring trans fatty acids are found in small amounts in the fat of meat and dairy products. Artificial trans fat comes from foods that contain partially hydrogenated oil formed when hydrogen is added to liquid oil turning it into solid fat (industrial fat).
Industrial (artificial) trans-fatty acids are detrimental, but ruminant-originated trans fatty acids have been reported as neutral or equivocal.
[http://www.ncbi.nlm.nih.gov/pubmed/23433578] Well-controlled observational studies and randomized trials indicate that trans fatty acid consumption adversely affects multiple risk factors for chronic diseases, including blood lipids and lipoproteins, systemic inflammation, endothelial dysfunction, and probably insulin resistance, diabetes, and adiposity. [www.ncbi.nlm.nih.gov/pubmed/19916363] A recent study using human liver cells found that trans fatty acids from the diet causes modifications in plasma cholesterol levels by inducing many adverse changes in several hepatic proteins and the hepatic membrane composition.
[http://www.ncbi.nlm.nih.gov/pubmed/24058537] Harvey, et al., showed that trans fatty acids incorporated into the plasma membranes at the expense of the saturated fatty
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acids, stearic, palmitic, and to a lesser extent, myristic acid. Both trans fats, t18:1n-9 and t18:2n-6, induced a pro-inflammatory response by elevating surface expression of intercellular adhesion molecule-1 (ICAM-1).  
Lipid peroxides  
Plasma membranes are one of the preferential targets of reactive oxygen species which cause lipid peroxidation. This process modifies membrane properties such as fluidity, a very important physical feature known to modulate membrane protein localization and function. [http://www.ncbi.nlm.nih.gov/pubmed/22940500] Numerous reports have established that lipid peroxidation contributes to cell injury by altering the basic physical properties and structural organization of membrane components. Oxidative modification of polyunsaturated phospholipids has been shown, in particular, to alter the intermolecular packing, thermodynamic, and phase parameters of the membrane bilayer. [http://www.ncbi.nlm.nih.gov/pubmed/16195227]  

In part 2 we will examine approaches to improve the state of membrane structure, confirming that the cell membrane can indeed be resuscitated, improving cellular function and patient health.

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