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Commentary on Biological Membrane: Unlimited Function & Limited Breakthrough

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Virtually every living cell evolves with (i) a self-replicating machinery, (ii) a matter and energy exchangeable system, and (iii) a microsphere barrier which is commonly known as biological membrane or biomembrane. In a cell, the self-replicating system duplicates the genetic materials and the membrane ensures the symmetrical distribution of those genetic materials so that each daughter cell receives the right share. On the other hand, the matter and energy exchangeable system warranty them for energy acquisition, growth and development, the membrane provides it by photosynthesis and respiration. In addition, the bio membrane controls how to sense the environment which allows the control movements of substances in and out. The whole process is multi-layered regulation and each layer is highly stringently regulated and controlled by bio-membrane.

A biomembrane is an enclosing membrane that functions as a selective barrier within or around a cell. Biological membranes are composed of phospho-lipid bilayer where the hydrophilic phosphate group faces toward inside and the outside of the cell whereas; the two fatty acids tails are aligned end to end make a hydrophobic barrier (a sandwich zone) inhibits the passage of ions, and polar molecules however, gaseous molecules such as O_2, CO_2, etc., can sneaks in due to constant rotational motion of non-polar fatty acid tails (between C-C single bond). In addition, this lipid bilayer are plugged in with several proteins, carbohydrates and cholesterol (absent in bacterial membrane and plant do have a similar type of steroid) and their relative distribution varies from membrane types. For examples, the plasma membrane has 50% each whereas in mitochondrion it has 25% lipid and 75% protein. This unique protein embedded lipid bilayer is called fluid mosaic model. A variety of biomembranes can separate cell from external environment: apical, basolateral, presynaptic and postsynaptic ones, membranes of flagella, cilia, microvillus, filopodia and lamellipodia, the sarcolemma of muscle cells, as well as specialized myelin and dendritic spine membranes of neurons. These membranes can also form different types of "supramembrane" structures such as caveola, postsynaptic density, podosome, invadopodium, desmosome, hemidesmosome, focal adhesion, and cell junctions. These types of membranes differ in lipid and protein composition.

The protein molecules are the unique components of the lipid bilayer whether in cell or the membrane bound organelles such as mitochondrion or chloroplasts, which sense the environments. There are three types of membrane proteins namely: (a) Integral membrane proteins - an α-helix hold by H-bonding between peptide bond and the hydrophobic side chains (R) spans the region between interior (cytoplasm or lumen for organelle) and exterior of the cell or organelle (b) Peripheral Membrane Proteins - they are held up on the periphery of the cell by H-bonding or by hydrostatic interaction with the integral proteins and distribution of those peripheral proteins changes often due to asymmetrical structure of membrane (c) Lipid Anchored Proteins: proteins are covalently bonded to the membrane.

In higher organisms, the membrane subdivided the cells into specific reaction center known as organelles and they are embedded with specific proteins. The membrane proteins contribute 25 - 30% of human genome which represents 3% of the total proteins and they do perform the following tasks in general: (i) adhesion; (ii) cell to cell communication; (iii) recognition; (iv) receptor; (v) transport; (vi) enzymes; (vii) energy conversion.

Nature's most spectacular creation is the energy transducing process viz. photosynthesis and respiration which occurred in the membrane of chloroplasts and mitochondria, respectively. Since the appearance of cyanobacteria which is about 2.6 billion years ago, earth experiences a radical changes in the atmosphere that is the evolution of free oxygen (from a reduced state to an oxidized state) and the synthesis of energy rich organic compounds. Today's research nailed down the major pathways of photosynthesis which occurred in thylakoid membrane of chloroplast (the light reaction: ATP synthesis, NADPH production and oxygen evolution) however; the *in vitro* synthesis of carbohydrate by using light and carbon dioxide is not yet achieved. In addition, any wavelength above the visible range such as infrared or microwave can initiate photosynthesis? This area of research is still wide open and needs more rethinking of membrane research. Furthermore, the second energy transducing organelle - mitochondria which is a membrane bound and reside in another membrane (sac within a sac) and recover the energy rich ATP – molecule from the photosynthetic products. And, the same mitochondrial membrane also performs another magnificent job which is apoptosis (programmed cell death). Questions still remains unanswered how the membrane potential changes? When to deliver Cytochrome C for apoptosis and when to recover ATP from organic food? Does it require remodeling of mitochondrial cristae?

Another major challenge to membrane scientists is the physiology of the blood brain barrier. The challenge in treating most brain disorders is overcoming the difficulty of delivering therapeutic agents to specific regions of the brain by crossing the blood-brain barrier (BBB). This barrier - a tight seal of endothelial cells that lines the blood vessels in the brain - is a physiological checkpoint that selectively allows the entry of certain molecules from blood circulation into the brain. The problem for scientists is that the BBB does not differentiate what it keeps out. BBB strictly limits transport into the brain through both physical (tight junctions) and metabolic (enzymes) barriers. With very few exceptions, only nonionic and low molecular weight molecules soluble in fat clear the BBB. For instance, alcohol, caffeine, nicotine and

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antidepressants meet these criteria. However, large molecules needed to deliver drugs do not. Thus, while the BBB naturally evolved in order to protect the brain from invasion of various circulating toxins and other harmful molecules, it also serves as a major impediment towards the brain-specific delivery of various diagnostic/therapeutic molecules needed for combating various neuronal disorders.

To date, delivery of therapeutic molecules into the brain often involves highly invasive techniques (like drilling a hole in the skull). The utter scarcity of techniques for brain-specific delivery of therapeutic molecules using non-invasive approaches has led researchers to increasingly explore the vast potential of nanotechnology toward the diagnosis and treatment of diseases/disorders incurable with present techniques.

Scientists have now reported a nanoparticle-based platform which 'tricks' the BBB into allowing the entry of the nanoparticle into the brain, using an approach that draws parallel to the 'trojan horse' concept. Certain proteins and peptides, such as the iron-transporting protein transferrin, are allowed free access across the intact BBB as they function as carriers of essential nutrients into the brain. By linking transferrin with rod-shaped semiconductor nanocrystals (quantum rods) - an up and coming diagnostic agent which can also multitask as carriers of therapeutic molecules - it was found that the transferrin helps the linked quantum rods to 'sneak' across the BBB into the brain. This finding can have significant potential implications towards the development of brain-directed nanoparticle based diagnostic and therapeutic agents using minimally invasive procedures.

Thus, the science of membrane biology is an ever challenging one, even today; it is a very difficult task to isolate intact cell membrane, visualization by EM or AFM and characterization for effective drug delivery and therapeutics, characterization of membrane protein s by crystallization and x-ray diffraction.

Membrane composition and its biochemistry are still puzzle today and needs to be exploring. For example, Archaea can survive at extreme environment such as hydrothermal vent (2000 meter below the sea surface where temperature is 400°C and 200 atmospheric pressure), high salinity, highly acidic pH, etc., whereas, a salmon can survive at extreme cold temperature and a plant shed their leaves when the temperature drop during fall. Where is the limit of membrane tolerance?

Membrane scientists will remain busy for a very long time and this field is sure to attract many a bright mind and future scientist who might be able to solve some of the problems challenging us today by using more advanced technology of the future.