Introduction to biological membranes

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Main textbook:

Molecular Biology of the Cell 5th edition

Alberts et al. Garlands eds.

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Biological membranes

- Allow COMPARTIMENTALIZATION
  - Plasma membrane defines the boundary of the cell
  - Intracellular membranes subdivide the cell into different compartments (organelles) that differ in composition (proteins, ions, pH, redox potential, electrochemical potential)
  - These compartments carry out different cellular functions
- Favor biochemical reactions
  - 2D instead of 3D diffusion favors encounter of metabolites

- Membranes are thin (5-7 nm), strong, non-elastic, self-sealing, flexible, deformable, hydrophobic barriers between aqueous compartments
- Composed of amphiphilic lipids (phospholipids) arranged as a bilayer.
  - See https://www.youtube.com/watch?v=lm-dAvbl330

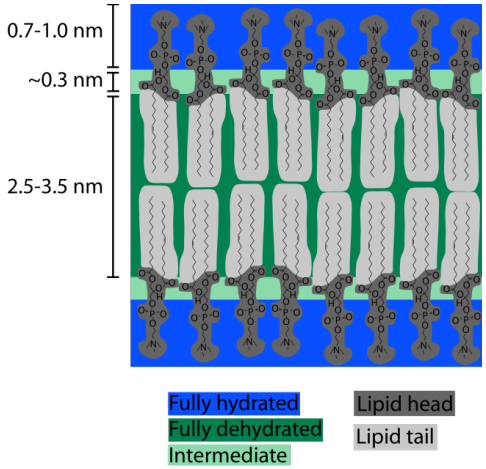


Figure 1: membrane bilayer

- The bilayers also contain non-membrane-forming lipids (see below), and proteins many of which carry carbohydrate moieties or covalently bound lipids.
- The bilayer is usually fluid, mostly liquid.

Membrane fluidity illustrated here

https://www.youtube.com/watch?v=jM_xePC70Yo

Challenges in membrane biology

- Membranes derive from membranes
  - membranes inherited from sperm and oocyte
  - how to make new membranes?
    - Growth: one molecule at a time (lipid/protein)
    - Fusion/fission
  - How to make the right amount of membrane?
    - Coordination between lipid and protein?
- How can the cell differentiate between two membranes?
  - E.g. what differs between an early and late endosome, how is that difference generated and maintained?
  - How can a protein be targeted to the right membrane?
- Limited permeability
  - How to selectively transport metabolites and nutrients when needed?
  - How to communicate across membranes?

Lipids in the membranes

Glycerolipids:

- A glycerol molecule **esterified** to two fatty acids and one phosphate

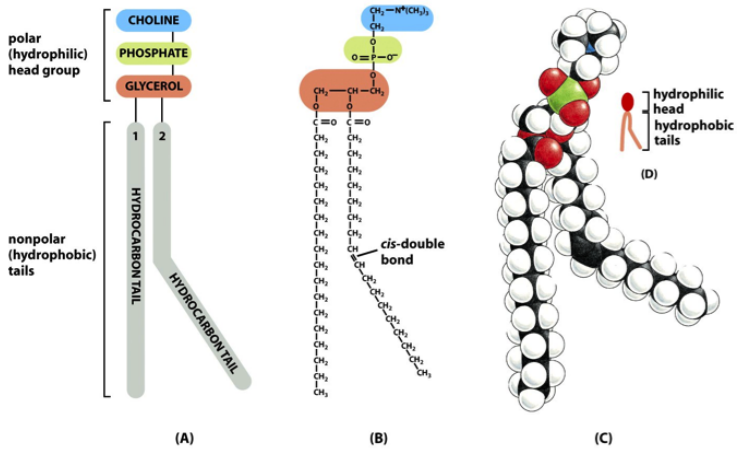


Figure 2: glycerolipid

Sphingolipids

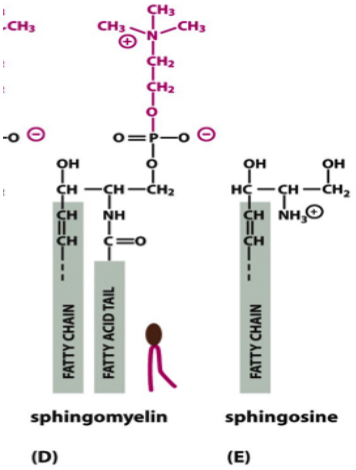


Figure 3: sphingolipids

- sphingosine is generated from serine and fatty-acid-CoA:

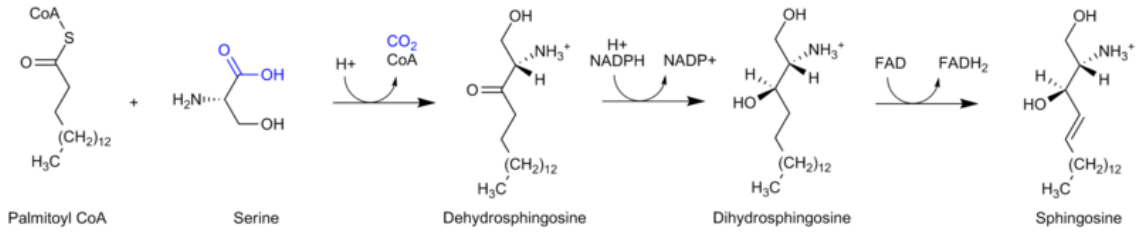
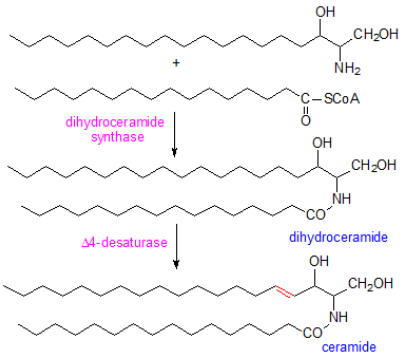


Figure 4: sphingosine biosynthesis

resulting in a long-chain base (LCB).

- Ceramide is generated through **amide bond** with free amino group:



Sterols

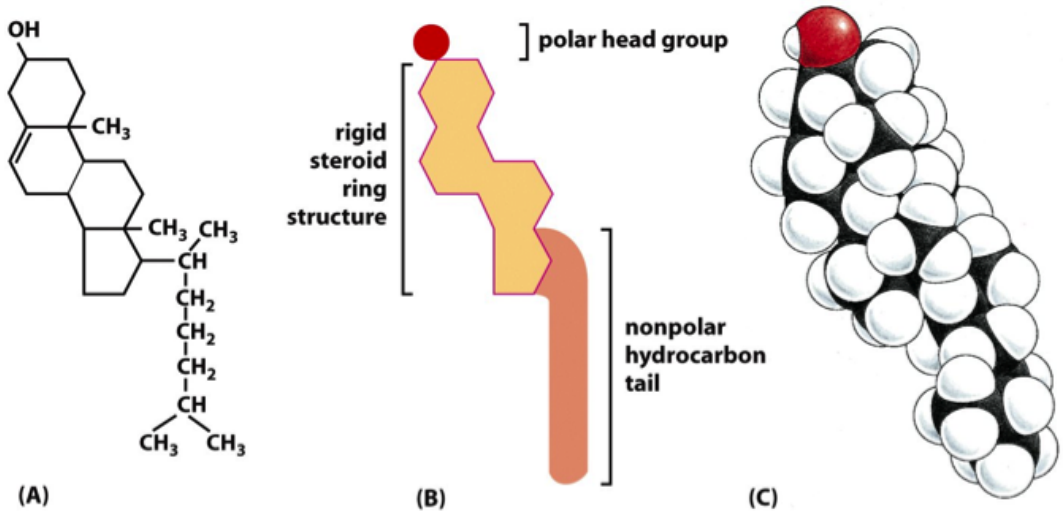
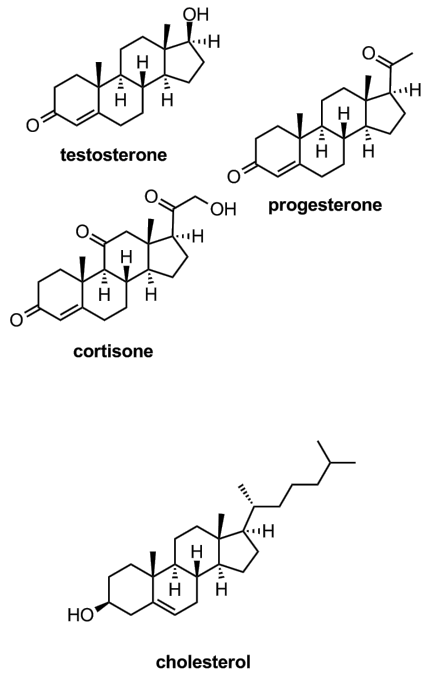


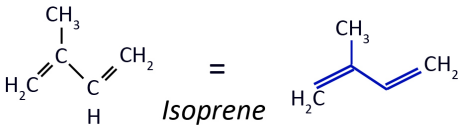
Figure 5: sterols



Cholesterol (in membrane) and steroid hormones (circulating) share a common structure, but the addition of the hydrocarbon tail to cholesterol makes it more hydrophobic and thus, makes it bind to membranes.

Figure 6: cholesterol vs. steroid hormones

Other lipids



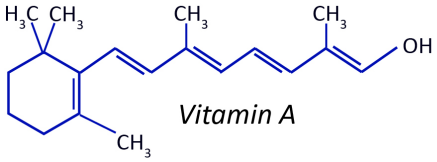


Figure 7: isoprenoids

- Isoprenoids

  (based on isoprenes)
  - geranyl-geranyl
  - farnesyl
  - ubiquinone
  - retinol (vit. A)
  - carotene
  - dolichol

  all relatively rare

Sterols are made from isoprenes:

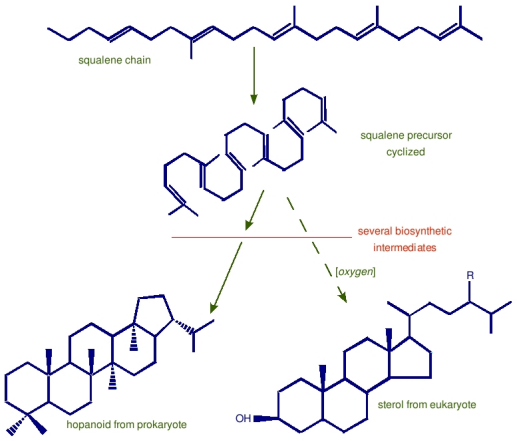
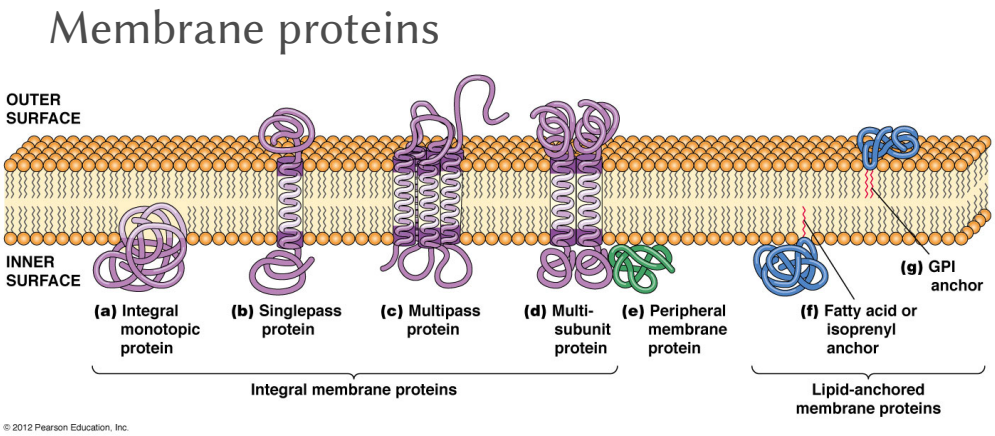


Figure 8: sterol biosynthesis



Transmembrane proteins

- Alpha-helical segments made of hydrophobic aminoacids
  - Membrane thickness is ~6nm, but the hydrophobic core is only ~3 nm. Each aminoacid in an alpha-helix is translated by 0.15 nm in the axis of the helix. Thus a transmembrane helix is around ~3/0.15= ~20 aminoacids.
  - Stretches of ~20 hydrophobic aminoacids can be detected using a hydropathy plot.
    - Hydropathy is calculated at each aminoacid position by averaging the hydropathy of all aminoacids between positions + and – 10 (**sliding window averaging**).
- Can be monotopic (one single TM domain) or polytopic (several TM domains).

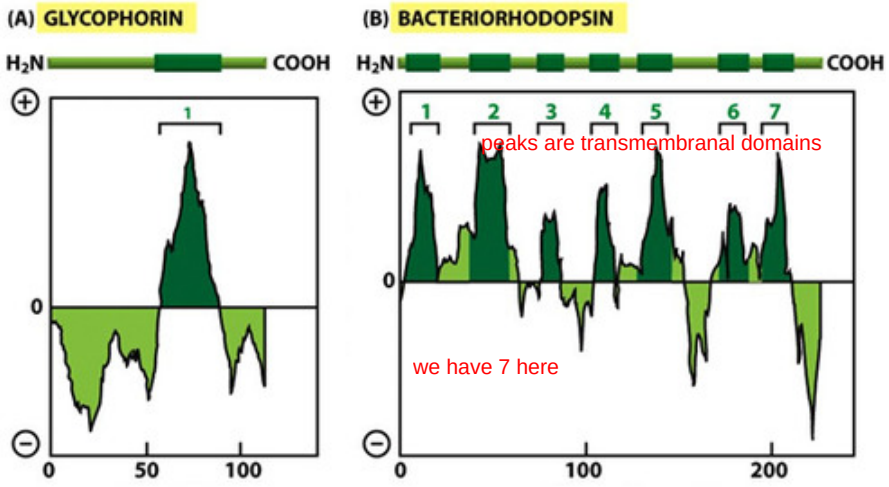


Figure 9: Hydropathy plots

Exceptions are beta-barrel integral proteins

- made of beta-sheets
- found in bacterial outer-membranes
- found in mitochondrial and chloroplasts outer membranes
  - endosymbiotic origin of organelles (bacterial origin).
  - Usually form pores

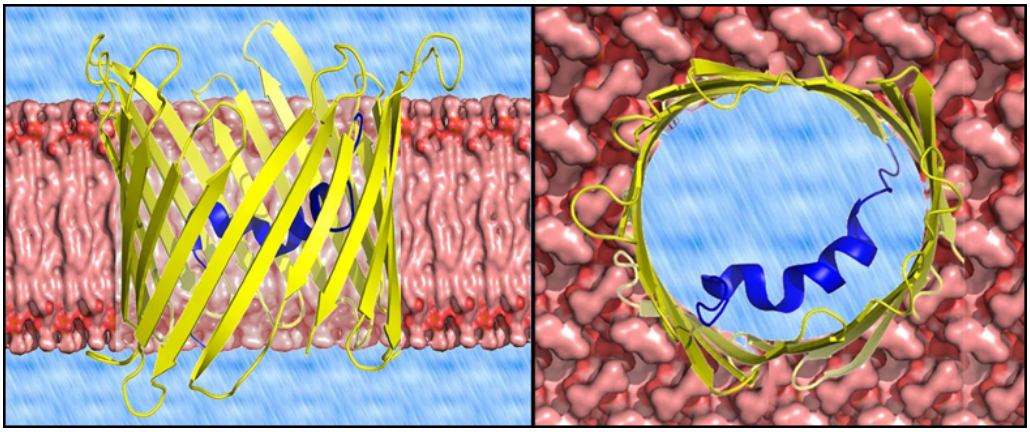


Figure 10: VDAC, a mitochondrial outer membrane protein

Lipidated proteins

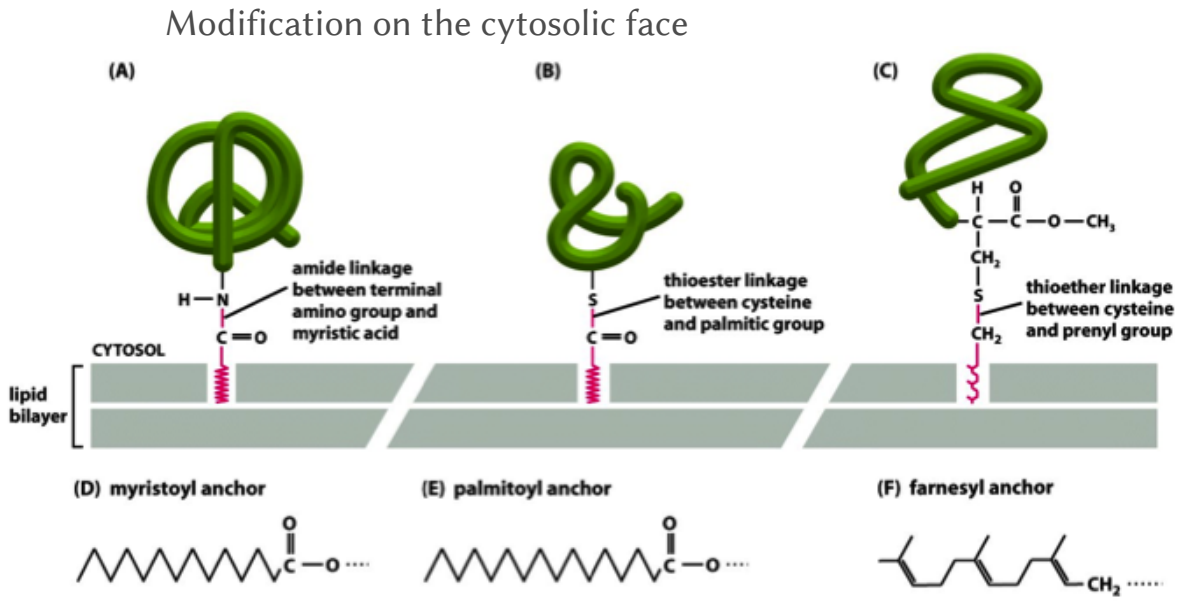


Figure 11: lipid protein modifications

Myristylation	C14 fatty acid via amide bond to amino group of N-terminal glycin	Added to co-translationally to cytosolic non membrane proteins, a permanent modification.	Sufficient for membrane binding only when combined with:1) Positive charge cluster,2) FA alkyl group, or 3) protein-protein interactions	Arf1 and c-src Exposed or hidden after reversible conformational change.
Fatty acylation	Typically C16 i.e. palmitic acid By thioester to cystein	Reversible modification in cis-Golgi, on soluble proteins and endodomains of trans-membrane proteins	Double FA-acyl group direct many proteins to lipid rafts	Caveolin, influenza hemagglutinin.
Prenylation	Farnesyl (C15) or geranylgeranyl (C20) By thioether to cystein	Added to cytosolic non membrane proteins. So called CaaX box usually at the C-terminus, a permanent modification	Often combined with nearby FA acyl groups	Two Ras isoforms: H ras farnesyl plus two FA acyl chains. K-ras Farnesyl plus cluster of positive charges

Importance of lipid Modifications

- They allow proteins to come on and off membranes and thus support dynamic processes during signal transduction, molecular sorting, membrane bending, vesicle formation, membrane recognition, etc.
- Functions and dynamics can be strictly regulated in time and place.
- Allow interaction of proteins with specific membranes only and with specific lipid micro-domains such as lipid rafts.

Modification on the extracellular side: GPI-anchor

Glyco phosphatidyl inositol (GPI) anchor addition	**Chemical composition**: PI Several sugar residues (N-acetyl glucose amine and mannose plus others) Phosphoethanolamine connected by amide bond to C-terminus of protein.	**Topology**: In the extracellular leaflet. The GPI anchor provides the only connection with the membrane.	**Distribution**: Enriched in apical membranes of epithelial cells, Enriched in lipid rafts. Tail can be removed by phospholipase C, releasing the proteins.	**Examples**: Thy-1 antigen Alkaline phosphatase Acetyl-choline esterase

Peripheral Proteins

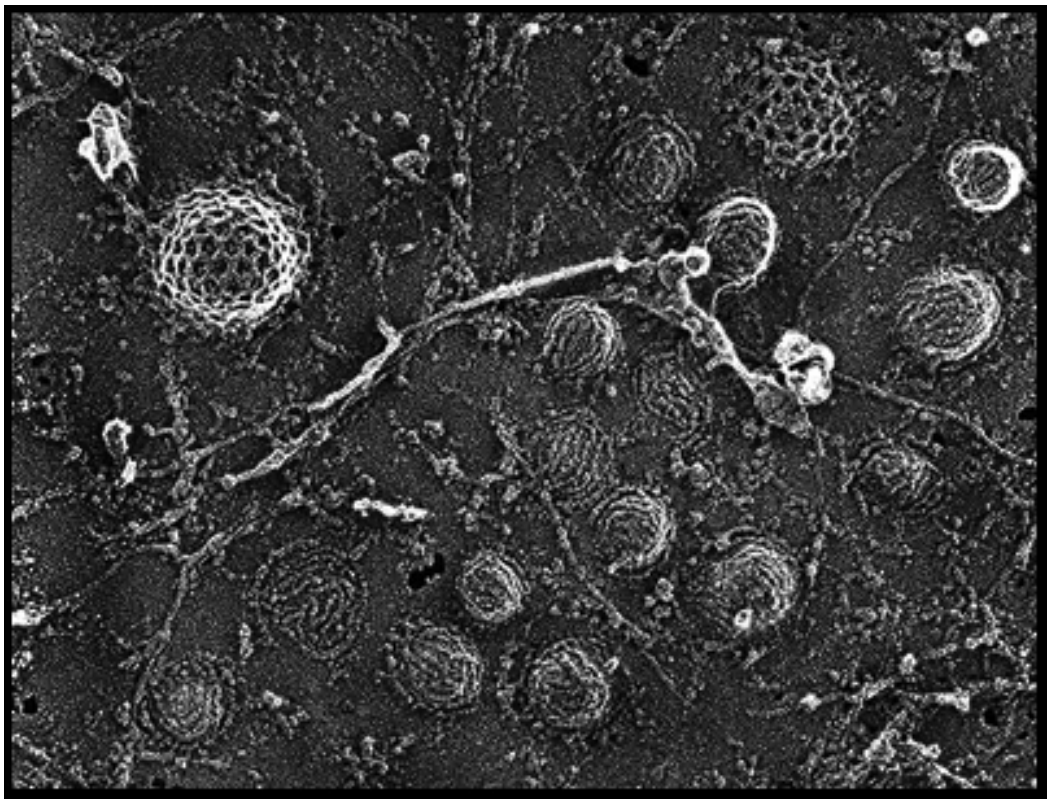


Figure 12: Cytosolic face of the plasma membrane

- Non-covalently attached to lipid head-groups or proteins in the membrane
- Complex mixture of proteins on both sides of a membrane
- Interactions are often transient and regulated
- Cytosolic side of PM is particularly rich in peripheral proteins: an extensive, dynamic 'cortex' of actin, adaptor proteins, and other proteins (needed for membrane stability; local membrane specializations; connections with cytoskeleton; transmission of signals; trafficking of vesicles; cell shape and polarity determination; membrane curvature; endocytosis....)

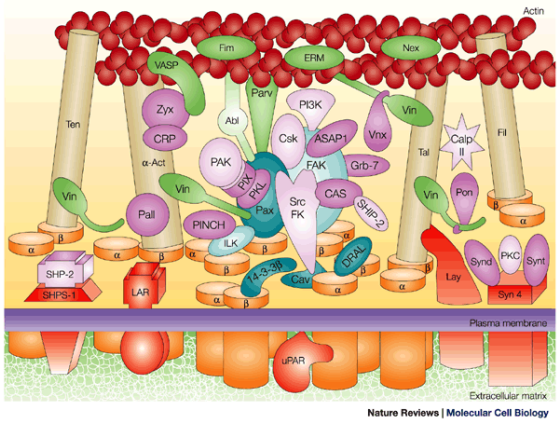


Figure 13: Focal adhesions: a peripheral protein network.