1 Membrane Proteins

- Have specific functions
- Associated with the lipid bilayer in different ways

Integral membrane proteins are located at the region where a protein penetrates or spans the lipid bilayer. If the lipid bilayer is spanned, a protein is called a transmembrane protein.

Peripheral membrane proteins associate with the phospholipid bilayer and with the penetrating proteins noncovalently.

Anchored proteins can be anchored with a sugar or a lipid.

1.1 Integral Membrane Proteins

Integral membrane proteins are amphipathic, with AA side chains being polar if the hydrophilic domains are aqueous. AA side chains are non-polar if the membrane-spanning domain is hydrophobic.

Single-pass transmembrane proteins have the shape of a single α-helix, while multipass transmembrane proteins have multiple α-helices.

Other structures can span the membrane as well.

A membrane spanning α-helix has 20 to 30 hydrophobic aminoacids. Not all α-helices, however, span the membrane.

e.g. receptors (with hydrophilic tails participating in intracellurar signalling), ion channels (conformational changes regulate permeability), β-barrel (a rigid rolled beta-sheet, wich play a role of some channels in bacteria, mitochondria, chloroplasts).

1.2 Techniques of Identification

- X-ray crystallography

  Precise identification of the 3D structure

- Hydrophobicity plots

  Segments of 20-30 hydrophobic amino acids spanning the lipid bilayer as an α-helix show as high peakson the graph of hydrophobicity agians the amino acid residue number.

1.3 Cell Membrane Proteins on One Sicde

Proteins can be anchored on the ctosolic face by an amphipathic α-helix.

1.4 Lipid-Anchored Membrane Proteins

GPI anchored proteins are synthesised in ER lumen and usually end up on the cell surface. Proteins with other lipid anchors, which are added by cytosolic enzymes, are directed to tho cytosolic face.

1.5 Extraction of Membrane Proteins

Peripheral membrane proteins use gentle extraction that does not destroy a lipid bilayer.

Integral membrane proteins destroy the membrane with detergents to extract the protein.

1.6 Lateral Diffusion of Membrane Proteins

- there is lateral diffusion within a leaflet
- no flip-flop

The protein movement can be studies with GFP (green fluorescent proteins).

1.7 FRAP (Fluorescence Recovery After Photobleaching)

1. First, proteins are labelled with a dye.
2. Then a spot is photobleached with a laser beam.
3. The bilayer is then recovered and the recovery time is then measured. If the recovery is faster, then the transmembrane proteins have lots of translative movement.

Movement via simple diffusion througth the lipid bilayer is such that down the concentration gradient the concentration drops

1.8 Impermeability of the Lipid Bilayer

These require membrane proteins for transportation.

1.9 Proteins Involved in Membrane Transport

- Multipass transmembrane proteins
  - create a protein-lined path across cell membrane
  - transport polar and charged molecules
- Each transport protein is selective
- Different cell membranes have a different complement of transport proteins

1.10 Passive and Active Transport

Passive transport is down the concentration gradient and hence does not require energy.

Active transport is the opposite.

Notice that there are two type of proteins: channel proteins (only passive transport) and transporter proteins (some do passive, some do active).

Channel proteins do not interact a lot with and do not bind strongly with the transported molecule. The conformation of channel proteins is also not changed a lot.

Transporter proteins are also called carrier proteins,

Both channel and transporter proteins are called transport proteins.

1.11 Resting Membrane Potential

A molecule with a positive charge has the greates motive force across the membrane, even though the concentration difference is the same for positive, negative and neutral molecules with the corresponding channel proteins.

1.12 Concentration Gradient and Membrane Potential

Electrochemical gradient is determined by the additive effect of the concentration gradient and the membrane potential (electrical gradient).

2 Channel Proteins

- hydrophilic pore across a membrane
- most channel proteins are selective
- passive transport
  - weak interactions with a solute
  - faster transport by channels than transporters, with several molecules passing when open

2.1 Ion Channels

There are two types of ion channels:

Non-gated Always open

e.g. K^+ leak channels, which are improtant in the plasma membrane of animal cells. They are also involved in determining the resting membrane potential.

Gated Only open on certain circuimstances

- Voltage-gated ion channel (change in the voltage across a membrane triggers the gate)
- Mechanically-gated ion channel (kept closed by a mechanical stress, opens if the plasma membrane is stretched)
- Ligand-gated (Extracellular ligand) (for example, neurotransmitters can trigger the gate)
- Ligand-gated (Intracellular ligand) (ions, nucleotides can open a gate)

3 Transporter Proteins

- bind a specific solute
- go through a conformational change that transports that solute across the membrane

One type of transporter proteins are uniporters:

- one molecule (with a passive transport down electrochemical gradient)

- direction of transport is reversible

e.g. GLUT uniporters (move glucose from a high concentration to low concentration down the electrochemical gradient, and can work in either directions, in and out of the cell)

Uniporters provide a passive transport with a transporter by facilitated diffusion.

3.1 Active Transport

- Active transport is against electrochemical gradient, which requires energy, but not necessarily in the form of ATP
  - Contransporters One molecule down the gradient, the second molecule against the gradient
  - ATP-driven pumps Involved ATP hydrolysis, moving molecules against the gradient
  - Light-driven pumps (bacteria) Use light energy, moving molecules against the gradient

3.2 Symporters and Antiporters

Symporters move two molecules in the same direction.

Antiporters move two molecules in opposite directions.

Free energy from co-transported ion moving down the electrochemical gradient is used to transport the 2nd molecule against its electrochemical gradient or to drive a secondary active transport.

Example 3.1

Na^+/glucose symporter moves Na^+ down the electrochemical gradient, which provides the energy to move glucose agains the concentration gradient. Cooperative binding of Na^+ and glucose leads to a conformational change in the protein.

Example 3.2

Most proteins require a spaciic pH (cytosol – neutral pH, lysosomes – acidic). Excess H^+ produced by acid forming reactions leaks into the cell, and then Na^+ direvn antiporters maintain cytosolic pH.

Example 3.3

Na^+/H^+ exchanger (antiporter) uses the free energy stored in the Na^+ electrochemical gradient to move H^+ out of the cell. It responds to cytosolic pH so that if pH drops, the transporter activity increases.

Na^+/glucose symporter and Na^+/H^+ exchanger use the energy stored in the Na^+ electrochemical gradient to move other molecules against their electrochemical gradients. Continued action would equalise the Na^+ gradient, if there is no external supply of Na^+. The electrochemical gradient is hence maintained by the Na^+/K^+ pump (a transport ATPase).

3.3 ATP-driven pumps

- P-type transport ATPases are phosphorylated
  - Na^+ and K^+ are moved against electrochemical gradients
  - Na^+ gradient is used to transport of nutrients (glucose) into cells and maintain the pH and cell volume.

3.3.1 The Pumping Cycle of the Na^+/K^+ Pump

1. ATP is bound to the pump, 3 Na^+ bind an open cytosolic pocket
2. The pocket closes preventing Na^+ escape
3. ATP hydrolysis occurs, the pump is phosphorylated, the release of ADP causes a conformational change to E2.
4. In E2 the binding pocket is exposed on the extracellular side, $3Na^+$ exit.
5. 2 K^+ bind
6. The pocket closes preventing K^+ release.
7. The pump is deposhporylated.
8. ATP binds the pump returning it to the E1 state.