MEMBRANE PROCESSES & SIGNALLING CASCADES

As they relate to Terms 1 and 4 of System 4

Robert Campbell April 2011

Introduction to Membrane Processes & Signalling Cascades:

Animal cells are enclosed in a phospholipid bi-layer membrane. The 'head' of a phospholipid is hydrophilic (attracted to water), while the hydrophobic 'tails' are repelled by water and are forced to aggregate toward the center between the two heads. The hydrophillic head contains the negatively charged phosphate group, and may contain other polar groups. The hydrophobic tail consists of fatty acid hydrocarbon chains. The hydrophobic tails line up toward each other, forming a membrane with hydrophilic heads on both sides facing the water inside and outside the cell membrane. This mosaic of lipid cell membrane can act as a solvent for many other substances and proteins embedded within it so that they can migrate laterally over the membrane.

The many proteins and other substances embedded, attached or adjacent to the cell membrane play essential roles in initiating chemical signalling cascades within the cell. Some act as chemical pumps to move potassium, sodium, calcium and hydrogen ions against a concentration gradient. Figures 2 and 3 illustrate typical arrangements of a great diversity of membrane related chemicals.

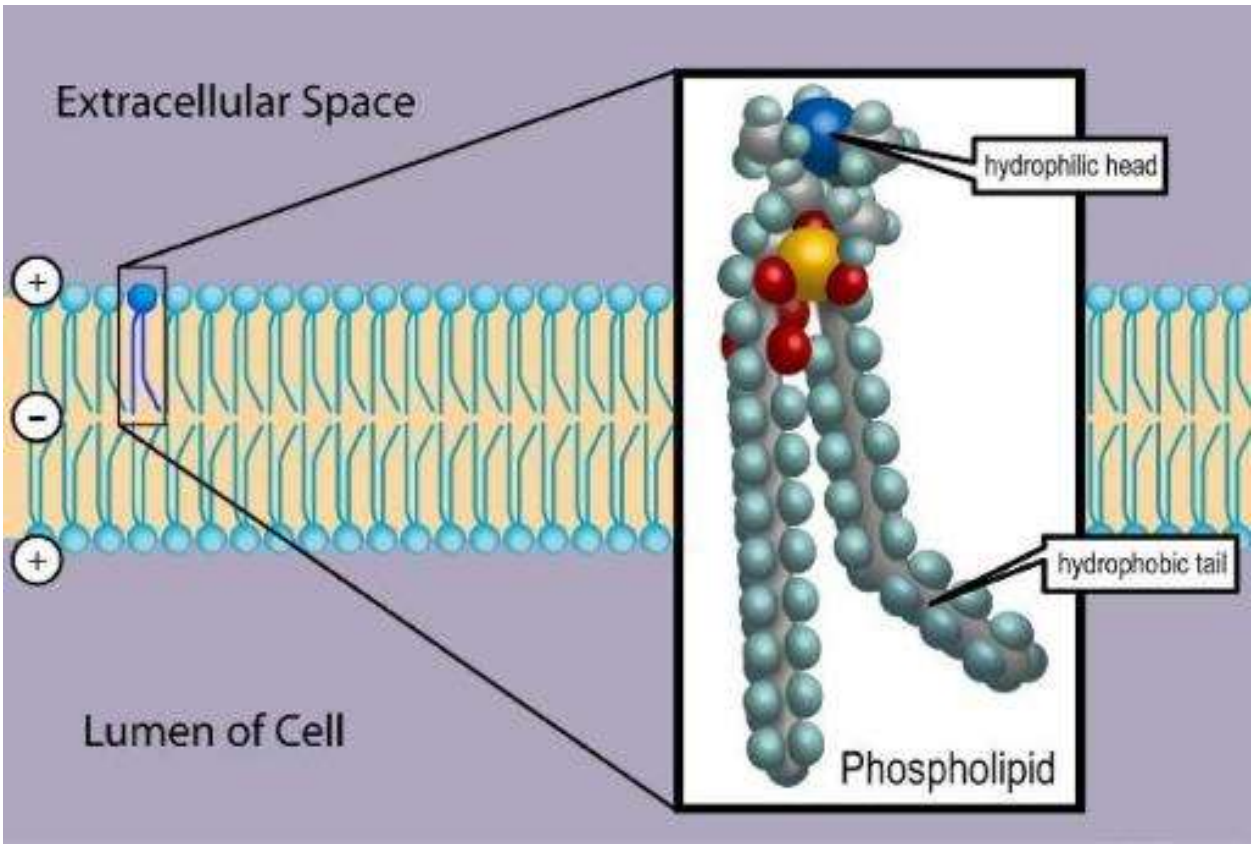


Fig. 1

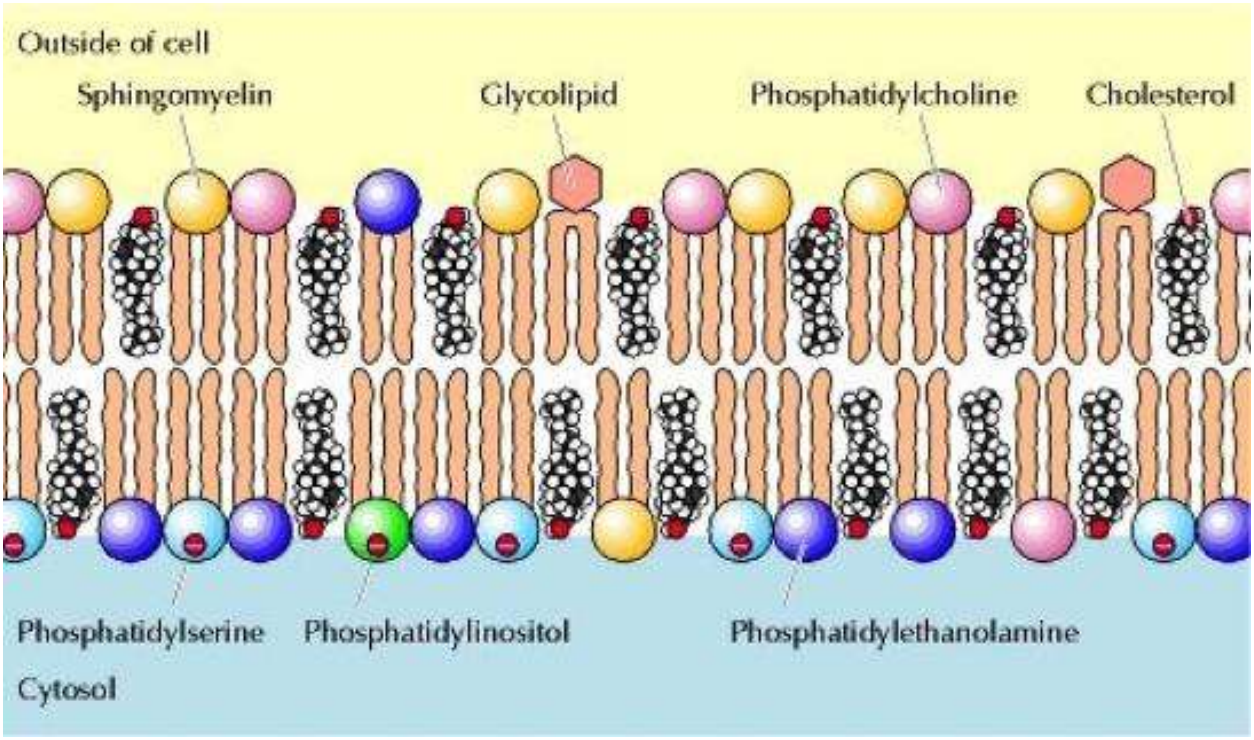
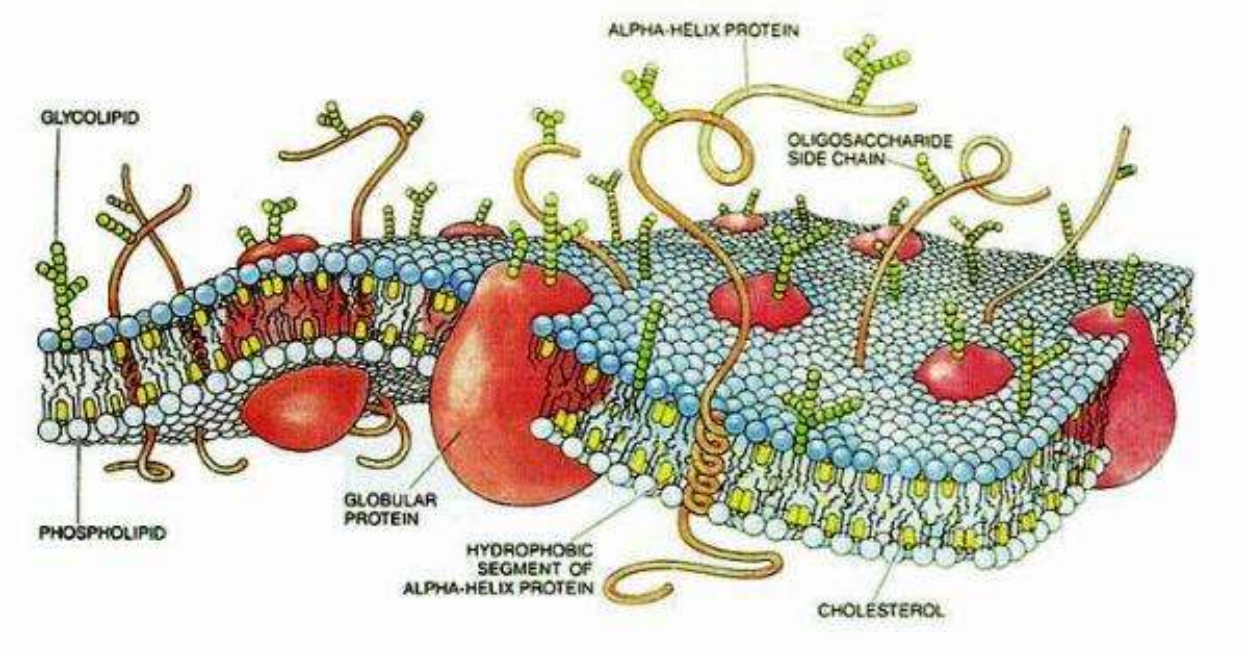


Fig. 2

The outer leaflet consists predominantly of phosphatidylcholine, sphingomyelin and glycolipids. The inner leaflet contains phosphatidylethanolamine, phosphatidylserine, and phosphatidylinositol. Cholesterol is distributed in both leaflets and adjusts the fluidity of the membrane. The phosphate heads have a net negative charge. Many proteins and other chemicals are also embedded as below.

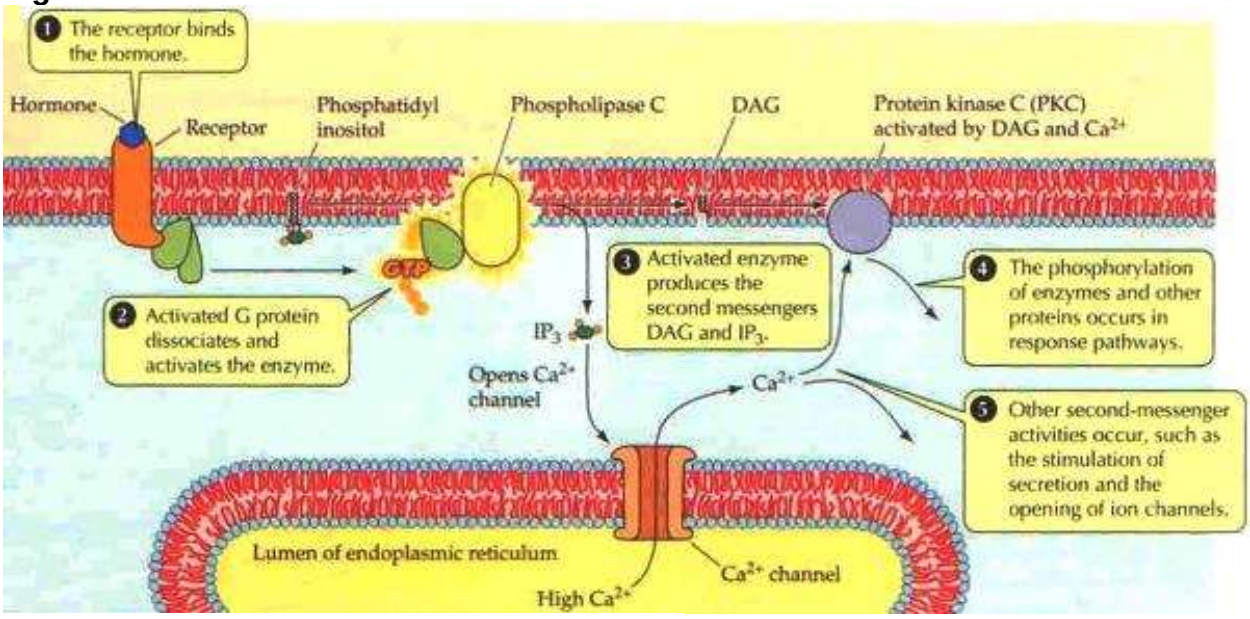
A few simplified examples of signalling pathwa



Some membrane proteins penetrate only part way through the membrane.

Peripheral membrane chemicals attach to other proteins and do not penetrate.

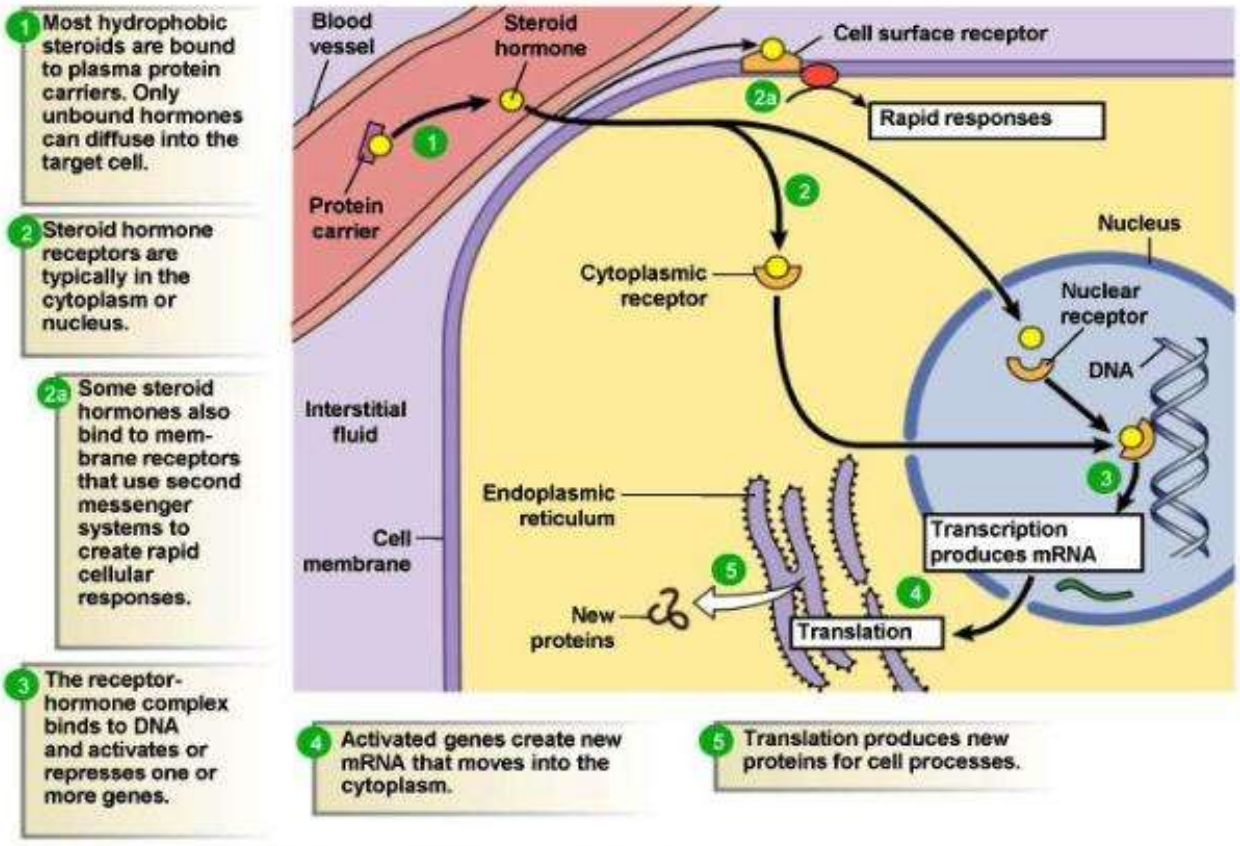
Fig. 3



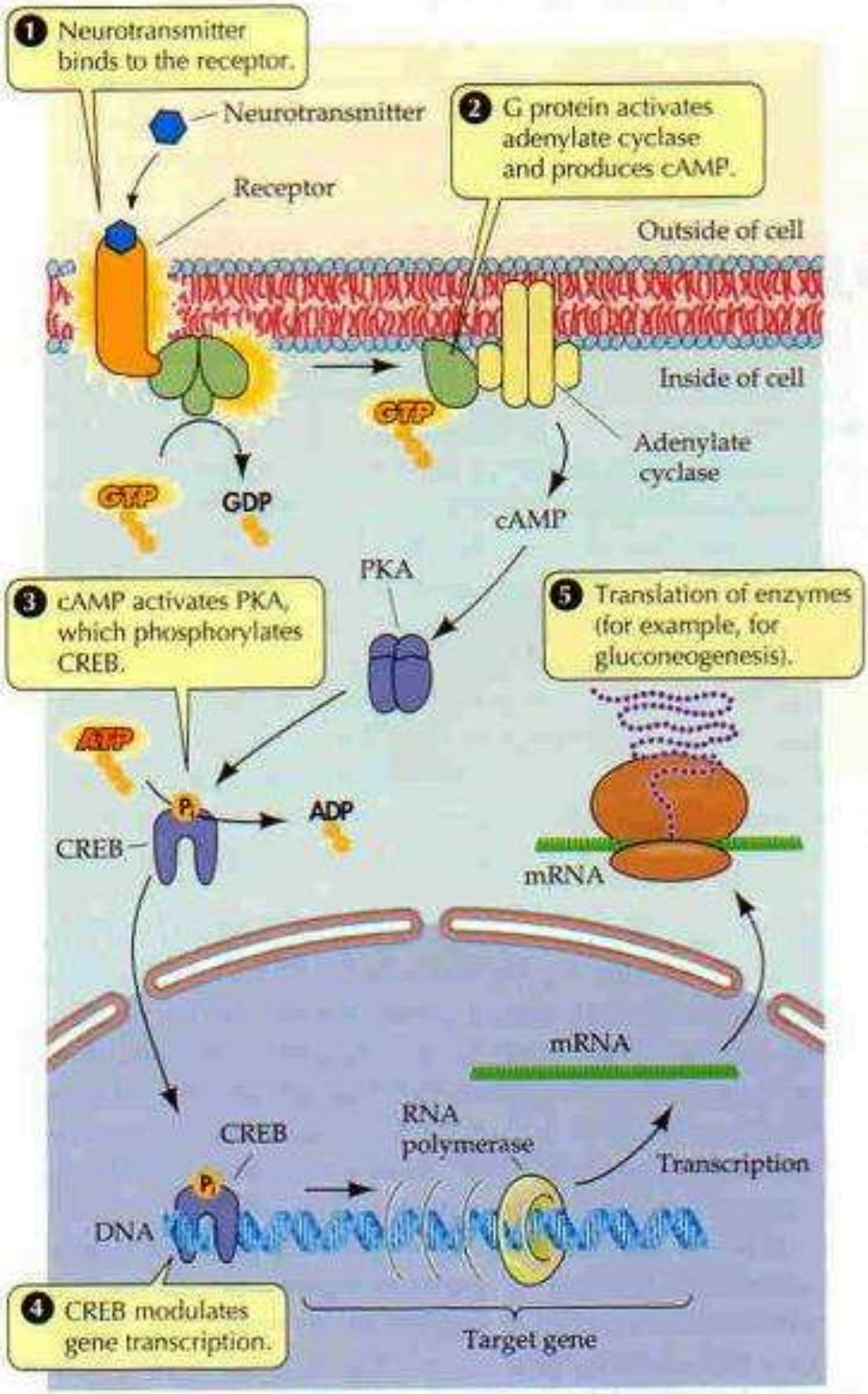
Calcium ions (Ca2+) previously pumped into and stored in the ER are rapidly released when Inositol triphosphate (IP3) opens the channel.

There are over 300 kinds of transport channels many acting as pumps to move ions and other chemicals against a concentration gradient.

Fig. 4



Steroid hormones derive from lipids and phospholipids mainly in the gonads and adrenal glands. They are lipid soluble and can pass through the membrane to receptors in the cell. Protein hormones such as insulin and growth hormone as well as monoamine hormones such as adrenaline cannot pass through the membrane. They must bind to a membrane receptor to initiate a signaling cascade to the nucleus.



38.16 Cyclic AMP Can Trigger Gene Expression PKA activated by cAMP can enter the nucleus and activate a transcription factor, CREB. CREB binds to the cAMP response element (CRE) and enhances gene expression.

Fig. 5

G proteins communicate signals from many hormones, neurotransmitters, and other signaling factors. The chemical signals are called ligands when they dock on a receptor. The ligand binding employs electronic forces, not covalent chemical bonds and docking is reversible.

When signal molecules dock on a receptor domain outside the cell it causes the embedded protein receptor to alter shape in an intracellular domain that activates a "peripheral" G protein at the inner membrane. The G protein activates a cascade of further compounds, and finally causes a change downstream in the cell.

G protein complexes bind to phosphate groups. G proteins (**guanine nucleotide-binding protein family**) respond to many signaling factors to activate signaling cascades downstream. They function as molecular switches. When attached to a complex with three phosphate groups (Guanosine triphosphate GTP) they turn on. When they are attached to a complex with only two phosphate groups (Guanosine diphosphate GDP), they turn off.

G proteins regulate metabolic enzymes, ion channels, transporters, and other parts of the cell machinery, controlling transcription, motility, contractility, and secretion, which in turn regulate systemic functions such as embryonic development, learning, memory, and homeostasis. PKA is a protein kinase that is activated by cyclic adenosine mono-phosphate (cAMP).

Cyclic AMP (adenosine monophosphate) is a second messenger, used for intracellular signal transduction, such as transferring the effects of hormones like glucogon and adrenaline, which cannot pass through the cell membrane. It is involved in the activation of protein kinase enzymes (PKA) that regulate the effects of adrenaline and glucagon. It also regulates the passage of Ca2+ through ion channels. cAMP is synthesized from ATP on the inner side of the plasma membrane.

Fig. 6
Phosphorylation:

Phosphorylation is the addition of a phosphate (PO4) group to a protein or other organic molecule and plays a critical role in cell signaling. (The agent of exchange is commonly Adenosine Tri-Phosphate (ATP) which can be reduced to ADP or AMP.) It activates or deactivates a great many protein enzymes, including some causing or preventing diseases such as cancer and diabetes. Each amino acid in protein contains a side chain, which distinguishes it from other amino acids. Phosphates are negatively charged so that their addition to a protein will change its characteristic shape through ionic (electronic) forces. Enzymes called kinases (phosphorylation) and phosphatases (dephosphorylation) are involved in switching other enzymes on or off by changing their shape. Within a protein, phosphorylation can occur on several amino acids usually serine, threonine or tyrosine. Histidine and aspartate phosphorylation sometimes occurs as part of two component pathway (analogous to stimulus-response to the environment common in prokaryotes). It is relatively uncommon in eukaryotic pathways.

There are thousands of different kinds of proteins in a cell and up to one half of them may be phosphorylated in some cellular state. Phosphorylation often occurs on multiple distinct sites on a given protein to alter its shape. Upon the deactivating signal, the protein enzyme becomes dephosphorylated again and stops working. This is a global mechanism in complex signaling cascades.

Phosphorylation and Energy:
Adenosine tri-phosphate (ATP) is the "high-energy" exchange medium in the cell. It is synthesized in mitochondria organelles by adding a third phosphate group to ADP (adenosine di-phosphate) in a process called oxidative phosphorylation. ATP is also synthesized by glycolysis that converts glucose into pyruvate, releasing free energy to form ATP and NADH (reduced nicotinamid adenine dinucleotide). Glucose is synthesized by solar energy in plant cells. Glycolysis in the cytoplasm produces pyruvate which is employed by mitochondria to convert the bulk of the energy originally in glucose to ATP via the citric acid (Krebs) cycle.

Figure 7 shows a couple of steps employing enzymes in a more complex process of energy conversion. Enzymes are proteins that fold into a highly specific shape. Various molecules are attracted and fit in such a way that they are brought into intimate contact and can bond together much more rapidly and accurately than they would at random. Enzymes are highly specific catalysts tailored to each chemical reaction. Enzymes can be turned on and off by attaching or removing phosphate groups. In some cases other molecules can attach to turn them off or turn them back on by their release in a reverse manner to phosphate groups.

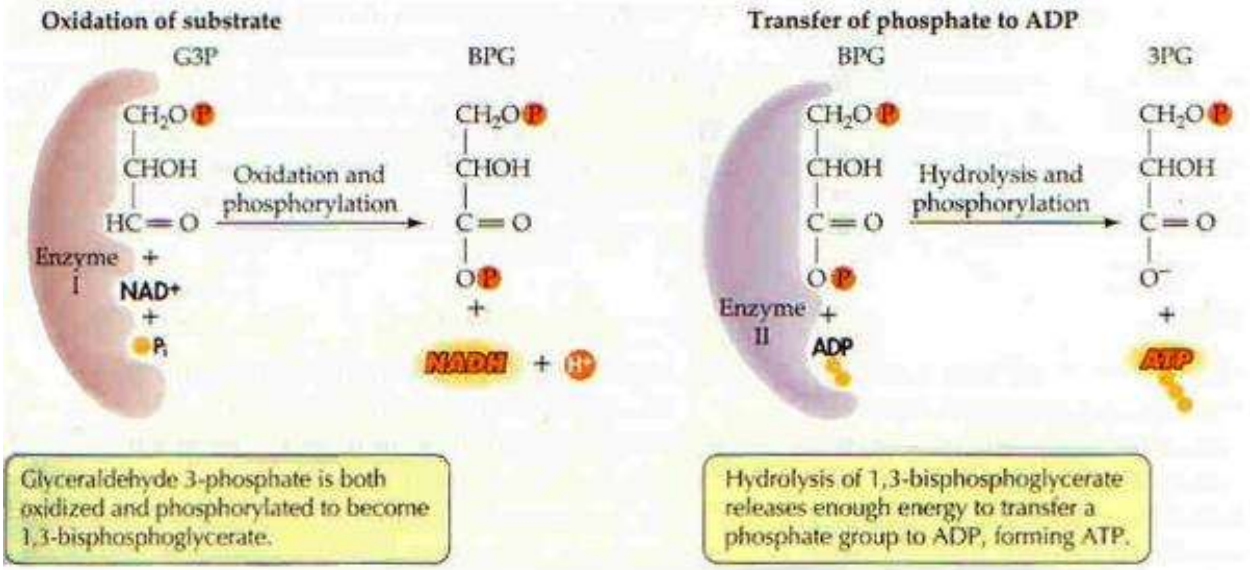
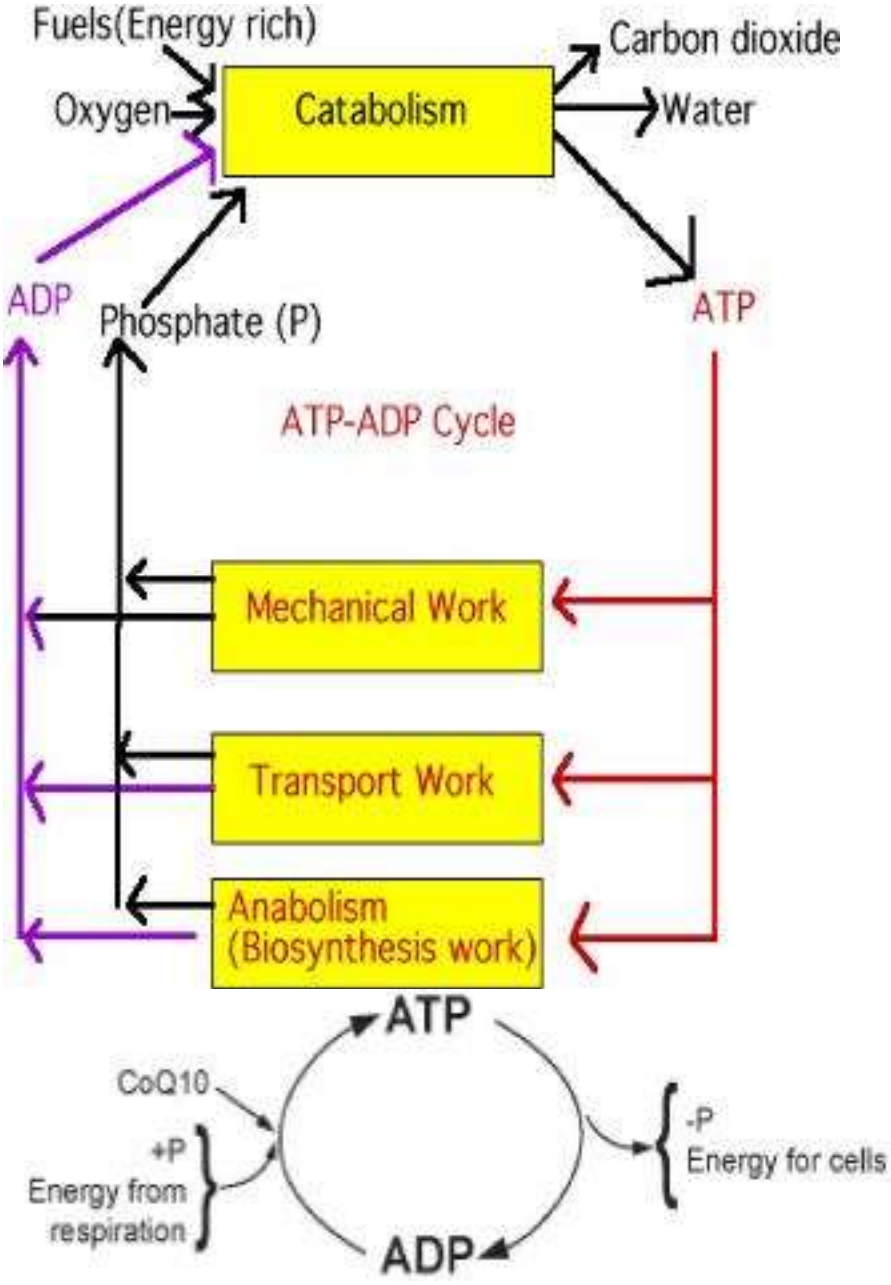


Fig. 7

Phosphorylation of sugars such as glucose is often the first stage of their catabolism in cells because the phosphate group prevents them from diffusing back outside through the membrane transporter. Catabolism is a metabolic process where complex organic compounds are broken down into simpler compounds, for instance converting glucose into carbon dioxide and water with the release of energy into ATP. Anabolism is the metabolic steps requiring energy to make complex compounds such as proteins by assembling simple compounds such as amino acids.

Figure 8 below gives a general picture of how the process works to provide the energy needed by cells to operate.


Fuels(Energy rich)
Oxygen
Catabolism
Carbon dioxide
Water
ADP
Phosphate (P)
ATP
ATP-ADP Cycle
Mechanical Work
Transport Work
Anabolism
(Biosynthesis work)
ATP
CoQ10
+P
Energy from
respiration
-P
Energy for cells
ADP

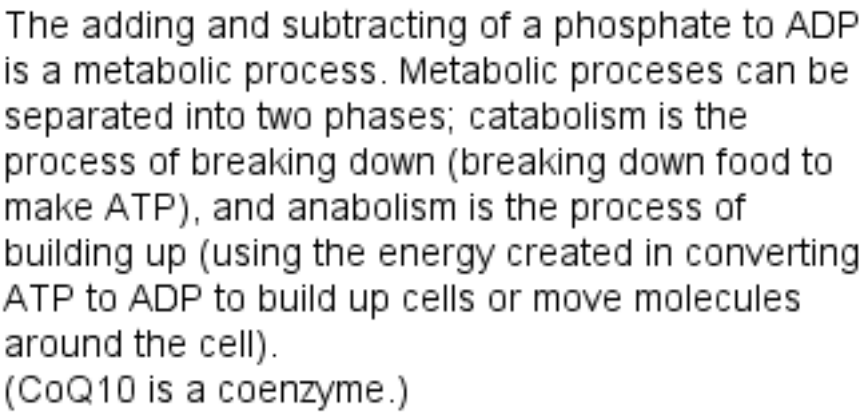


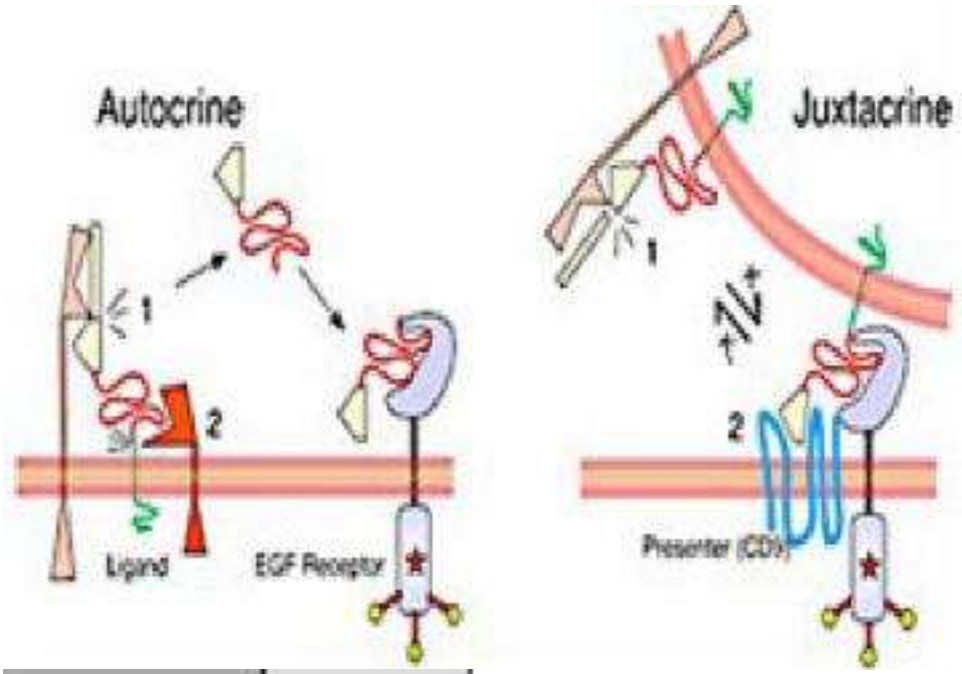
Fig. 8
Endocrine, Autocrine, Paracrine, & Juxtacrine Signalling:

Endocrine signalling cascades are initiated by chemical messengers released from the endocrine glands. They circulate in the blood stream and bind to chemical receptors embedded in the membranes of various cells throughout the body that in turn initiates a series of events that results in a signalling cascade to the nucleus. Chemical messengers can also inhibit signalling cascades or the cascade may depend on their concentration or other factors.

Autocrine signalling releases a chemical messenger to the outside a cell that binds to a receptor in the same cell to initiate or modify a signalling cascade in that cell.

Juxtacrine signalling docks a signalling chemical directly with the chemical receptor on an adjacent cell. The signalling chemical remains attached to the sending cell. An example of juxtacrine signalling is shown in the "Notch" signal represented above right in Figure 9.

Paracrine signalling releases chemical messengers that rapidly degrade or are reabsorbed over very small distances, such as at synaptic junctions between neurons.


Autocrine
Juxtacrine
1
2
Ligand
EGF Receptor
Presenter (CD)

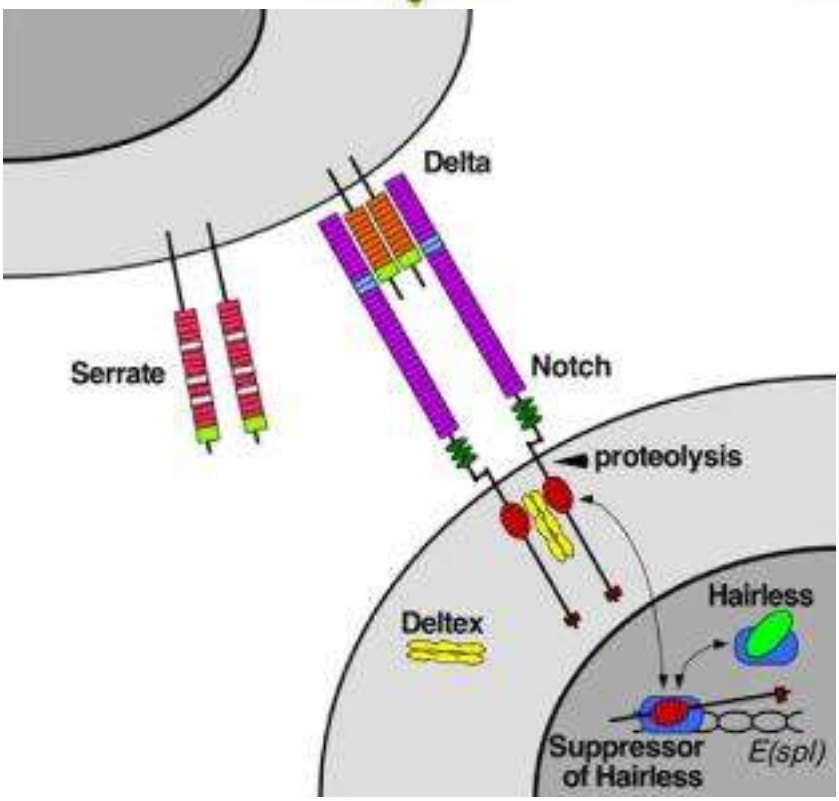

Delta
Serrate
Notch
proteolysis
Deltex
Hairless
Suppressor
of Hairless
E(spl)

Fig. 9

Other Signalling Mechanisms:

Because **calcium ions (Ca2+)** are an important "second messenger" that affects all cell signalling, it is essential to keep concentrations very low in the cytosol so as not to interfere with other signalling cascades unless it is needed rapidly. PMCA is a membrane transport protein that employs ATP to move calcium against a steep concentration gradient to the outside of the cell or into organelles where it is sequestered for rapid release when needed. Calcium ions also bind with protein buffers that shape enzymes while reducing the amount of free calcium in the cytosol. When calcium is bound with the small buffer calmodulin, transport is accelerated. Sodium-Calcium Exchanger pumps (NCX) are needed to remove calcium ions faster, especially in excitable neuron and muscle cells. Calcium has a vital and ubiquitous influence on cell signalling of all kinds in cells of all kinds.

Sodium-potassium (Na+K+) pumps move these two ions in opposite directions across the plasma membrane to maintain a membrane resting potential. Three sodium ions are moved out by hydrolyzing ATP and two potassium ions move in. Potassium can leak back out while sodium ions cannot leak in. The sodium concentration outside the cell membrane provides the driving force for several secondary active transporters which import glucose, amino acids, and other nutrients into the cell as illustrated in Figure 10. Another important function of the Na+-K+ pump is to maintain the volume of the cell. Most proteins inside the cell are negatively charged and collect positive ions around them. Osmosis of water into the cell would cause it to swell unless checked.

The membrane protein pump transporter can also relay extracellular signaling into the cell. The downstream phosphorylation events include the activation of mitogen-activated protein kinase (MAPK) signal cascades, mitochondrial reactive oxygen species (ROS) production, as well as activation of phospholipase C (PLC) and inositol triphosphate (IP3) receptor (IP3R) in different intracellular compartments. Hydrogen peroxide and nitric oxide are also important in cell signaling.

Signal peptides are amino acid sequences that direct proteins (synthesized in the cytosol) to organelles such as the nucleus, mitochondria, endoplasmic reticulum(ER) and peroxisomes. A Signal Recognition Particle (SRP) shuttles between the ER and the cytosol and binds to the signal peptide on the leading end of the peptide string as soon as it is synthesized by a ribosome to chaperone the ribosome to the ER. The SRP detaches when the signal peptide guides the protein string to thread inside through an ER membrane translocator pore as it is assembled. Most ER signal peptides are relayed on to the Golgi Apparatus. A nuclear localization signal (NLS) is a peptide directing cytosol protein to the nucleus. The nucleolus is targeted by a nucleolar localization signal (NOS). The mitochondrial targeting signal (MTS) directs to mitochondria. PTS1 and PTS2 direct to peroxisomes.

Gap junctions are protein pores joining some cells in direct contact. This allows some small molecules and ions to diffuse from one cell to another. Gap junctions can be opened or closed by internal conditions in the cells depending on circumstances.

Some small molecules and ions can passively diffuse through the membrane by processes such as osmosis. Other membrane transport mechanisms involve endocytosis and exocytosis as reviewed later.

Complex Multi-Component Signaling Pathways:

Complex multi-component signaling pathways provide opportunities for feedback, signal amplification, and interactions inside one cell between multiple signals and signaling pathways. For example many growth factors bind to receptors at the cell surface and stimulate cells to progress through the cell cycle and divide. Several of these receptors are kinses that start to phosphorylate themselves and other proteins when binding to a chemical messenger or ligand. This phosphorylation can generate a binding site for a different protein and thus induce protein-protein interaction.

An example is given in Figure 11. The ligand (epidermal growth factor EGF) binds to the receptor called EGFR. This activates the receptor to phosphorylate itself (see the small P attached). The phosphorylated receptor binds to an adapter protein (GRB2), which couples the signal to further downstream signaling processes. For example, one of the signal transduction pathways that are activated is called the mitogen-activated protein kinase (MAPK) pathway. The MAPK protein is an enzyme, a protein kinase that can attach phosphate ions to target proteins such as the transcription factor MYC and, thus, alter gene transcription and, ultimately, cell cycle progression. Many cellular proteins are activated downstream of the growth factor receptors (such as EGFR) that initiate this signal pathway.

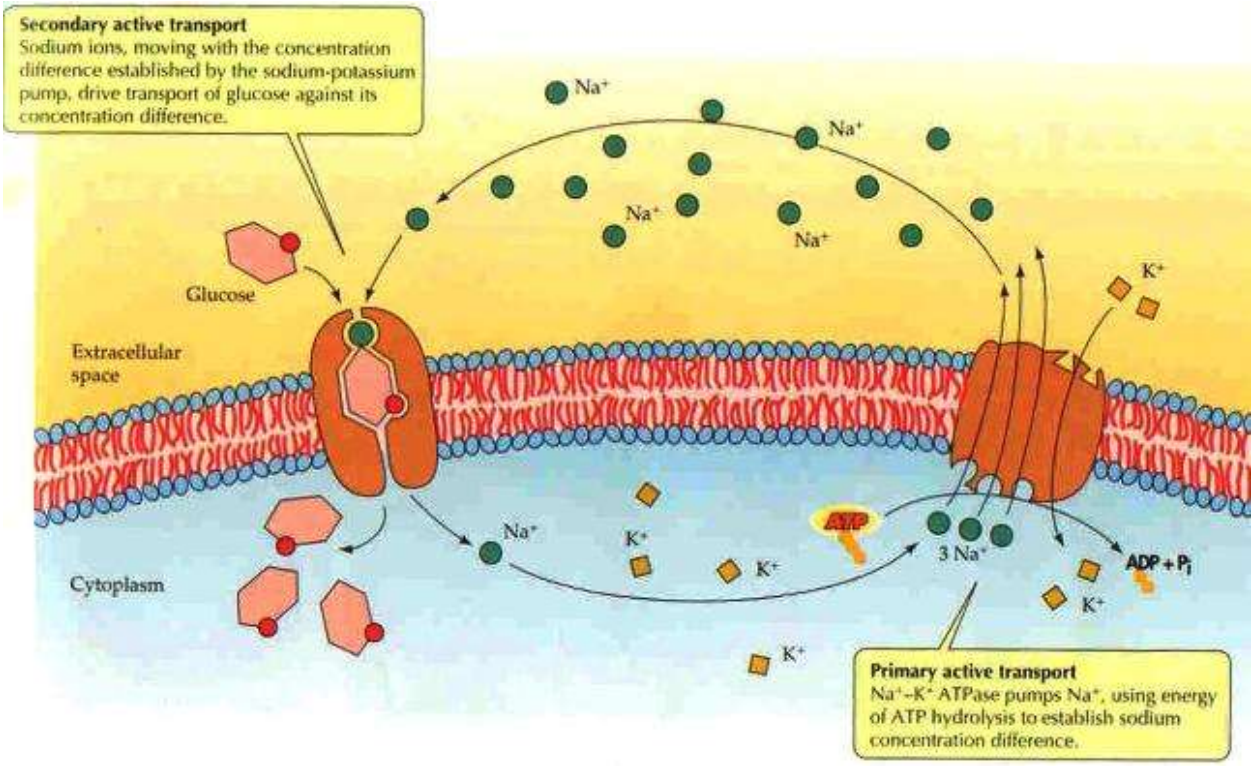
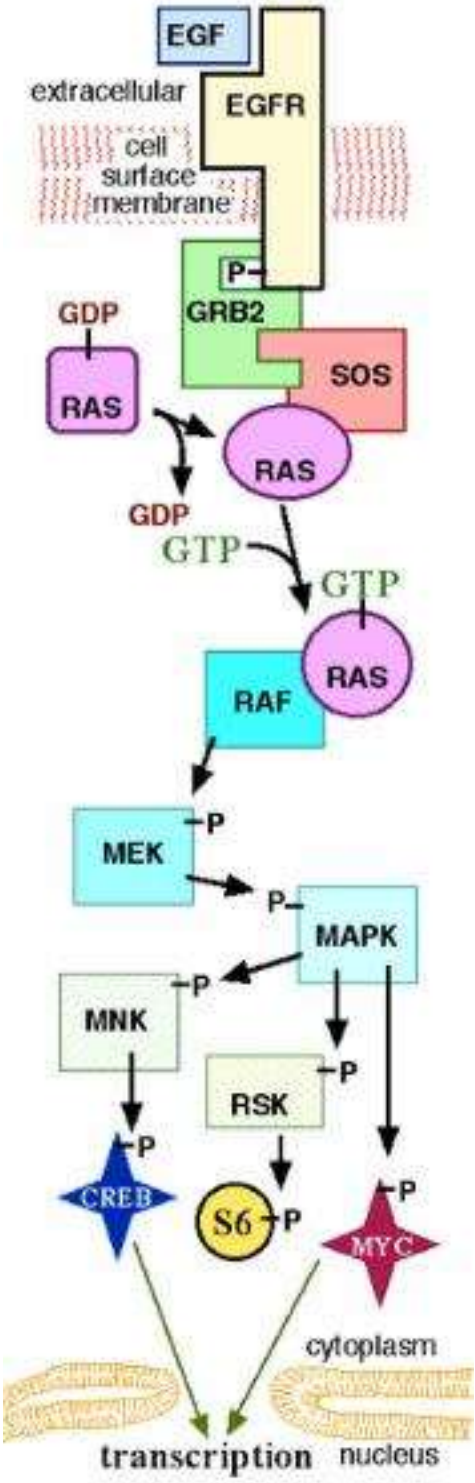


Fig. 10

Active transport of sodium & potassium ions (right) powers secondary active transport of glucose, amino acids, and growth factors stored in the extracellular matrix where protease enzymes break down some proteins into amino acids essential for protein synthesis in the cell.


EGF
extracellular
EGFR
cell
surface
membrane
P
GRB2
SOS
GDP
RAS
RAS
GDP
GTP
GTP
RAS
RAF
P
MEK
P
MAPK
P
MNK
P
RSK
P
CREB
S6
P
P
MYC
cytoplasm
transcription
nucleus

Epidermal growth factor EGF acts by binding with high affinity to epidermal growth factor receptor (EGFR) on the cell surface and stimulating the intrinsic protein-tyrosine kinase activity of the receptor to phosphorylate. This initiates a signal transduction cascade (via GRB2) that results in a variety of biochemical changes within the cell - a rise in intracellular calcium levels, increased glycolysis and protein synthesis, and increases in the expression of certain genes including the gene for EGFR - that ultimately lead to DNA synthesis and cell proliferation.

Activated Ras activates the protein kinase activity of RAF kinase. RAF kinase phosphorylates and activates MEK. MEK phosphorylates and activates a mitogen-activated protein kinase (MAPK). RAF, MEK, and MAPK are all serine/threonine selective protein kinases.

In the technical sense, RAF, MEK, and MAPK are all mitogen-activated protein kinases. MAPK was originally called "microtubule-associated protein kinase" (MAPK). One of the first proteins known to be phosphorylated was a microtubule associated protein (MAP). Many additional targets for phosphorylation by MAPK were later found, and the protein was re-named. The series of kinases from RAF to MEK to MAPK is an example of a protein kinase (phosphorylation) cascade. Such series of kinases provide opportunities for feedback regulation and signal amplification.

In simpler terms, the mitogen (EGF) binds to the membrane ligand. This means that Ras (a GTPase) can swap its GDP for a GTP. It can now activate MAP3K (e.g., Raf), which activates MAP2K, which activates MAPK. MAPK can now activate a transcription factor, such as myc.

Fig. 11

In some cases, receptor activation caused by ligand binding to a receptor is directly coupled to the cell's response to the ligand. For example, the neurotransmitter GABA can activate a cell surface receptor that is part of an ion channel. GABA binding to a GABAA receptor on a neuron opens a chloride-selective ion channel that is part of the receptor. GABA A receptor activation allows negatively-charged chloride ions to move into the neuron, which inhibits the ability of the neuron to produce action potentials. However, for many cell surface receptors, ligand-receptor interactions are not directly linked to signaling or to the cell's response. The activated receptor must first interact with other proteins inside the cell before the end physiological effect of the ligand on the cell's behavior results. Often, the behavior of a complex chain of interacting cell proteins is altered following receptor activation.

Some signaling transduction pathways respond differently depending on the amount of signaling received by the cell. For instance, the hedgehog protein activates different genes, depending on the amount of hedgehog protein present.

In summary complex multi-component signal transduction pathways provide opportunities for feedback, signal amplification, and interactions inside each cell between multiple signals and signaling pathways.

Some signaling molecules can function as both a hormone and a neurotransmitter. For example, epinephrine and norepinephrine can function as hormones when released from the adrenal gland and are transported to the heart by way of the blood stream. Norepinephrine can also be produced by neurons to function as a neurotransmitter within the brain. Estrogen can be released by the ovary and function as a hormone or act locally via paracrine or autocrine signaling. Active species of oxygen and nitric oxide can also act as cellular messengers. This process is dubbed redox signaling.
Complex Insulin Signaling Pathways:

A few of the insulin signaling pathways are shown in Figure 12. They include the regulation of glucose and lipid metabolism, cell growth, differentiation, and general gene expression.

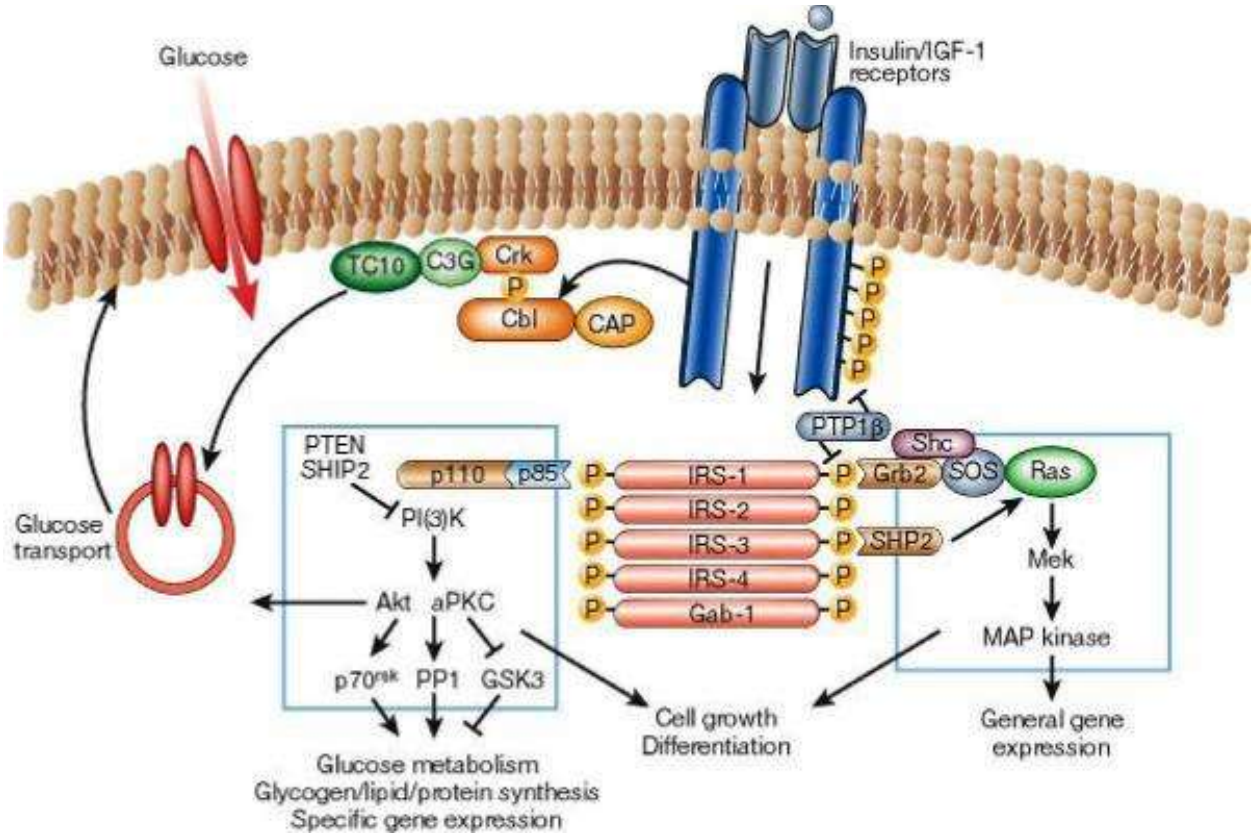

Glucose
Insulin/IGF-1 receptors
TC10
C3G
Crk
P
Cbl
CAP
P
P
P
P
P
PTP1β
Shc
Grb2
SOS
Ras
PTEN
SHIP2
p110
p85
PI(3)K
IRS-1
IRS-2
IRS-3
IRS-4
Gab-1
SHP2
Mek
MAP kinase
Glucose transport
Akt
aPKC
p70rsk
PP1
GSK3
Cell growth
Differentiation
General gene expression
Glucose metabolism
Glycogen/lipid/protein synthesis
Specific gene expression

Fig. 12

Endocytosis and Exocytosis:

Membrane transport systems such as diffusion and pumps are not sufficient to meet all the needs of cells. Endocytosis is needed to ingest needed raw materials in the required quantities and exocytosis is needed to export cell products and dispose of waste. The general methods of endocytosis are illustrated in Figure 13.

Phagocytosis is facilitated by phagocyte surface receptors that attach to ligand coated particles such as nutrients, microorganisms and proteins. In the immune system it is a major mechanism used to remove pathogens and cell debris. Bacteria, dead tissue cells, and small mineral particles are all examples of objects that may be phagocytosed. The resulting phagasomes eventually fuse with lyosomes which contain over 40 kinds of enzymes that digest the contents for use in the cell and discharge waste products by exocytosis.

Pinocytosis usually occurs at highly ruffled regions of the plasma membrane. The resulting vesicles capture extracellular fluid, molecules and dissolved food in a non-specific manner. The fluids captured include all solutes present. The cell engulfs already dissolved or broken down food. They fuse with other vesicles such as endosomes and lyosomes.

Receptor mediated endocytosis occurs at coated pits on virtually all cells such that the resulting vesicle has a specific protein coat that identifies it. The coat may be made up of a complex of clathrin proteins in the cytosol. Coated pits can concentrate large extracellular molecules that have different receptors for many ligands such as low density lipoprotein (LDL), transferrin (iron uptake), growth factors, antibodies and many others. Receptor mediated endocytosis is also actively implicated in transducing signals from the cell periphery to the nucleus.

Caveolae are another type of coated membrane cave-like buds, which exist on the surface of many, but not all cell types. They have a cholesterol-binding protein caveolin with a membrane enriched in cholesterol and glycolipids. They can constitute up to a third of the plasma membrane area of some cell tissues, such as smooth muscle of the gut. The uptake of extracellular molecules is specifically mediated via receptors in caveolae.

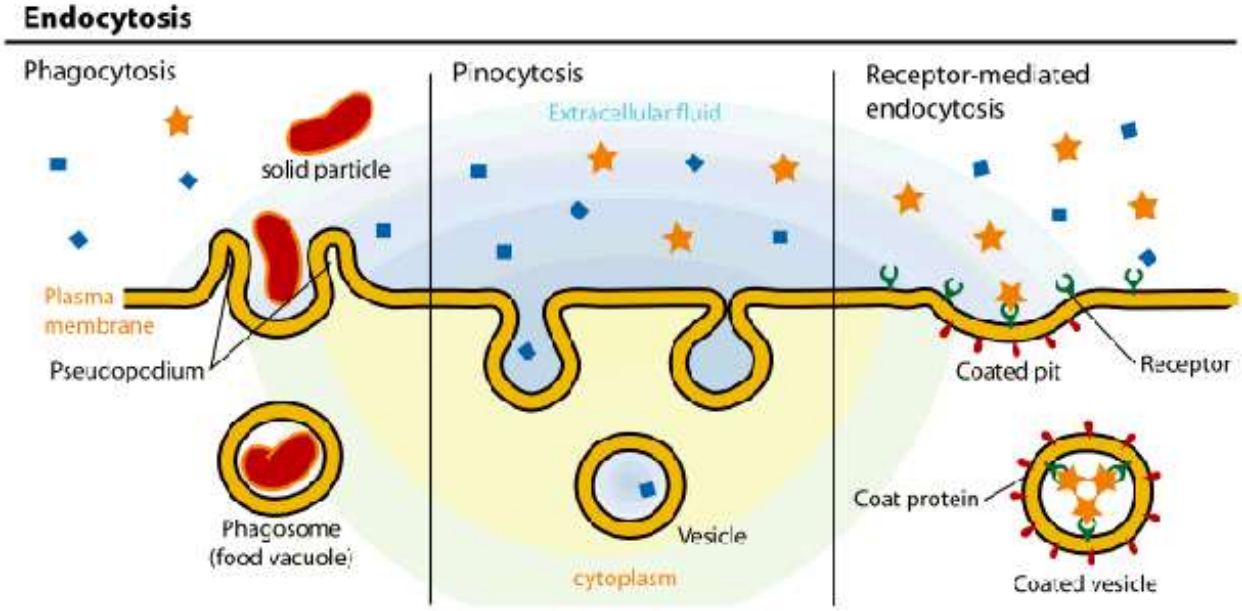
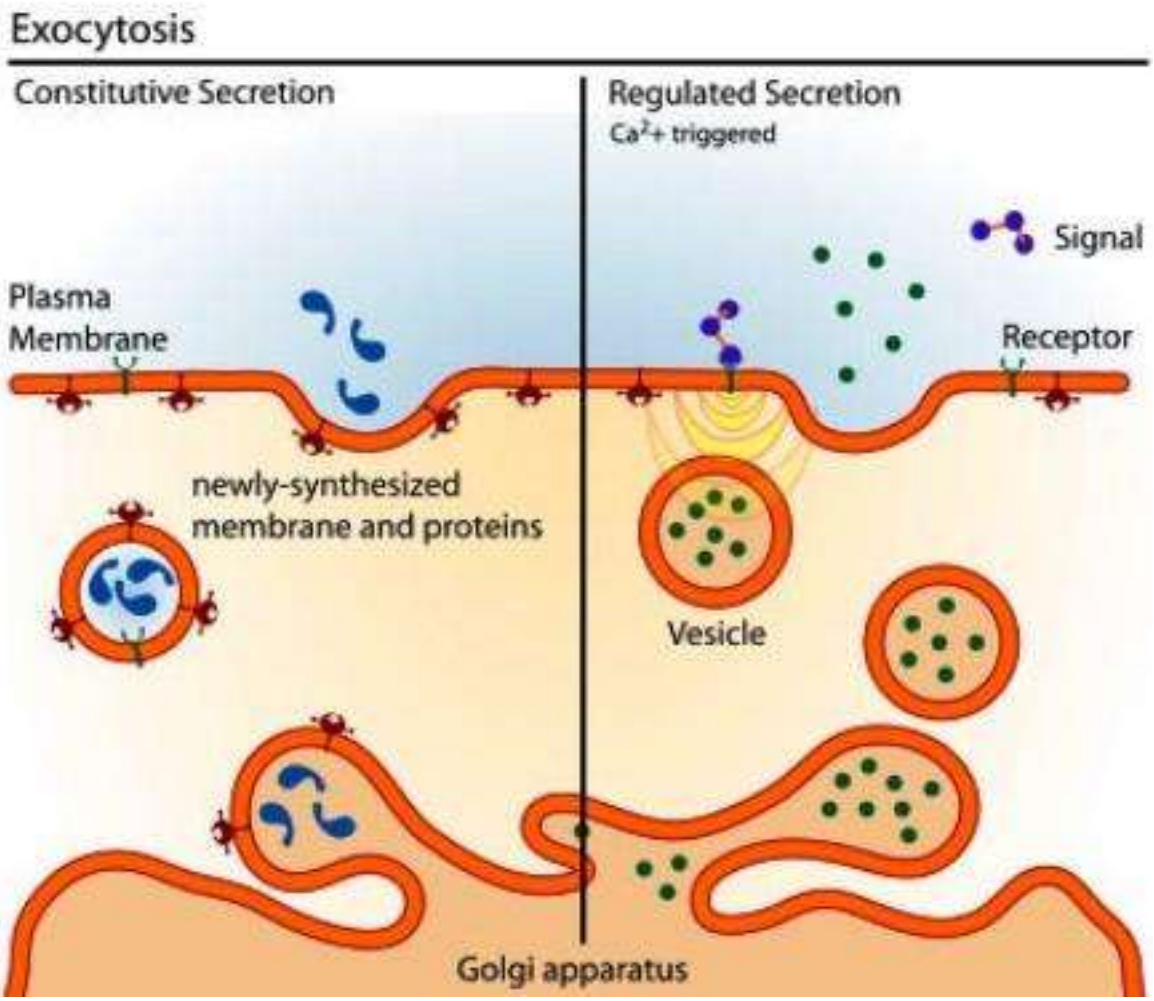
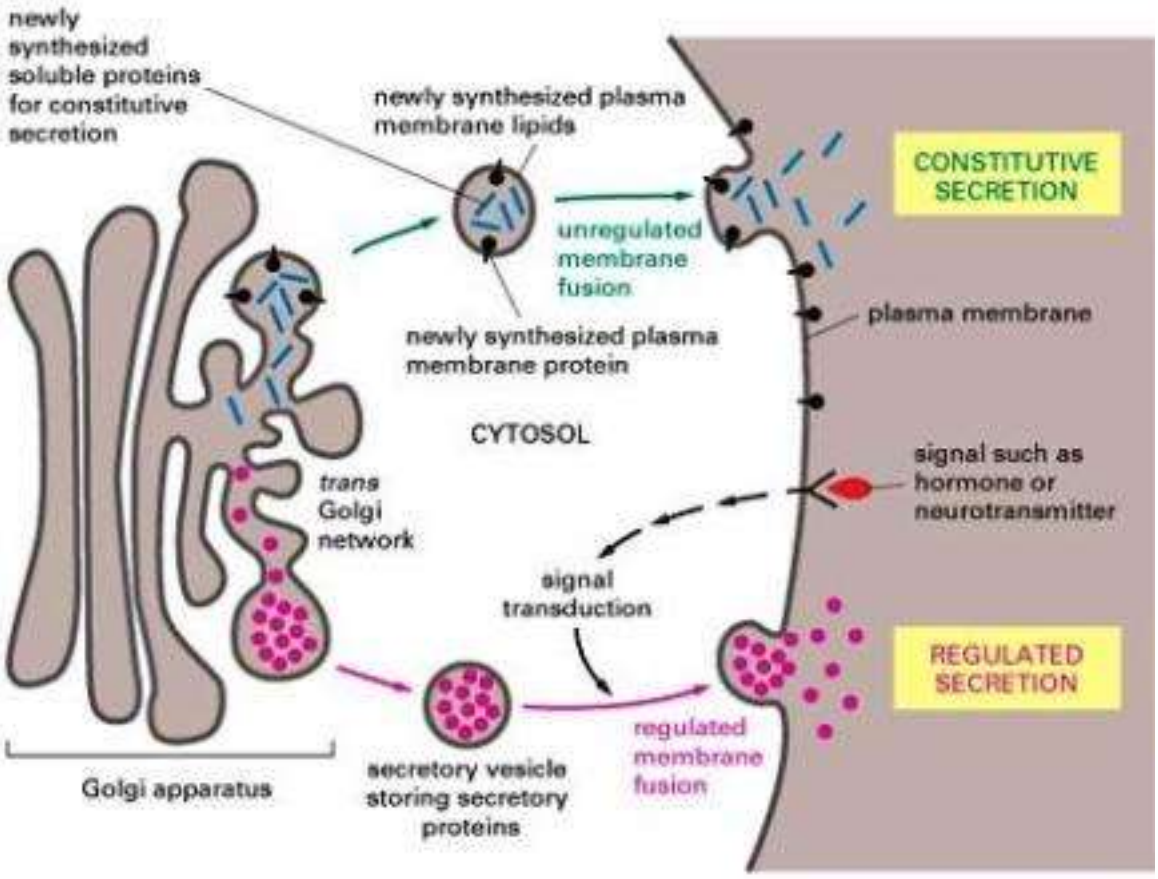


Fig. 13
Many cells in the body use exocytosis to release enzymes or other proteins such as signaling molecules that act in other areas of the body. For instance, clusters of α-and β-cells in the islets of Langerhans in the pancreas secrete the hormones glucagon and insulin, respectively. These enzymes regulate glucose levels throughout the body. As the level of glucose rises in the blood, the β-cells are stimulated to produce and secrete more insulin by exocytosis. When insulin binds to liver or muscle, it stimulates uptake of glucose by those cells. Exocytosis from other cells in the pancreas also releases digestive enzymes into the gut.

Nerve cells communicate across synaptic junctions by releasing neurotransmitters stored in vesicles near the synaptic cleft. The action potential of a firing neuron signals the vesicle to make contact with the plasma membrane and secrete their contents into the synaptic cleft for the other neuron to receive the chemical messenger. Components of the vesicle and extra neurotransmitter molecules are quickly taken up and recycled by the neuron to form new vesicles that are ready to send another pulse to an adjacent neuron. Neurons need to send many signals each second, which indicates how tight the controls are that regulate exocytosis.

An immune cell communicates with a virally infected cell that it must destroy itself to preserve other cells around it. An infected cell displays viral by-products on its surface, like turning on red warning lights to attract immune cells. Immune cells, such as the killer T cells wander throughout the body. They recognize and position themselves so that their plasma membranes are very close. In a rapid succession, the killer T cells mobilize secretory vesicles filled with enzymes, like perforin and granzyme B, adjacent to the inner side of their plasma membranes. In response to a signal, the vesicles undergo exocytosis and release their contents. These enzymes punch holes in the plasma membrane of the infected cell. This causes the cell to undergo self-destruction or apoptosis, also known as programmed cell death, to prevent further spread of the virus.


Exocytosis
Constitutive Secretion
Regulated Secretion
Ca2+ triggered
Signal
Plasma Membrane
Receptor
newly-synthesized membrane and proteins
Vesicle
Golgi apparatus


newly synthesized soluble proteins for constitutive secretion
newly synthesized plasma membrane lipids
CONSTITUTIVE SECRETION
unregulated membrane fusion
plasma membrane
newly synthesized plasma membrane protein
CYTOSOL
signal such as hormone or neurotransmitter
trans Golgi network
signal transduction
REGULATED SECRETION
regulated membrane fusion
secretory vesicle storing secretory proteins
Golgi apparatus

Lyosomes are produced by the Golgi Apparatus. They contain a complement of enzymes that digest the contents of phagosomes after they merge. The products such as sugars and amino acids diffuse from the fused lyosome for use in the cell and the waste products are removed from the cell by exocytosis.

Membrane fusion requires energy and the interaction of special "adaptor" molecules present on both the vesicle and plasma membrane. The adapter molecules are highly selective and only allow vesicles to fuse with membranes of particular organelles, thus preventing harm to the cell.

Once the appropriate adapter molecules bind to each other (docking), energy stored and released by ATP forms a fusion pore between the vesicle membranes and plasma membrane. The contents of the vesicle are released to the exterior of the cell (or the interior of an organelle such as a mitochondrion or another vesicle) as the fusion pore widens.

The vesicle ultimately becomes part of the plasma membrane or is recycled back to the cytoplasm. Vesicle formation can be very rapid.

Fig. 14
Membrane Merging:
Figuure 15 illustrates the action of SNARE proteins docking a vesicle for exocytosis. Complementary versions of the protein on the vesicle and the target membrane bind and wrap around each other, drawing the two bilayers close together in the process. Membrane fusion can be induced preferentially by Ca2+ or Mg2+ ions at various threshold concentrations for different phospholipid species of membrane. The lipid membranes must also be in a fluid state that may be transiently induced by ion concentrations.

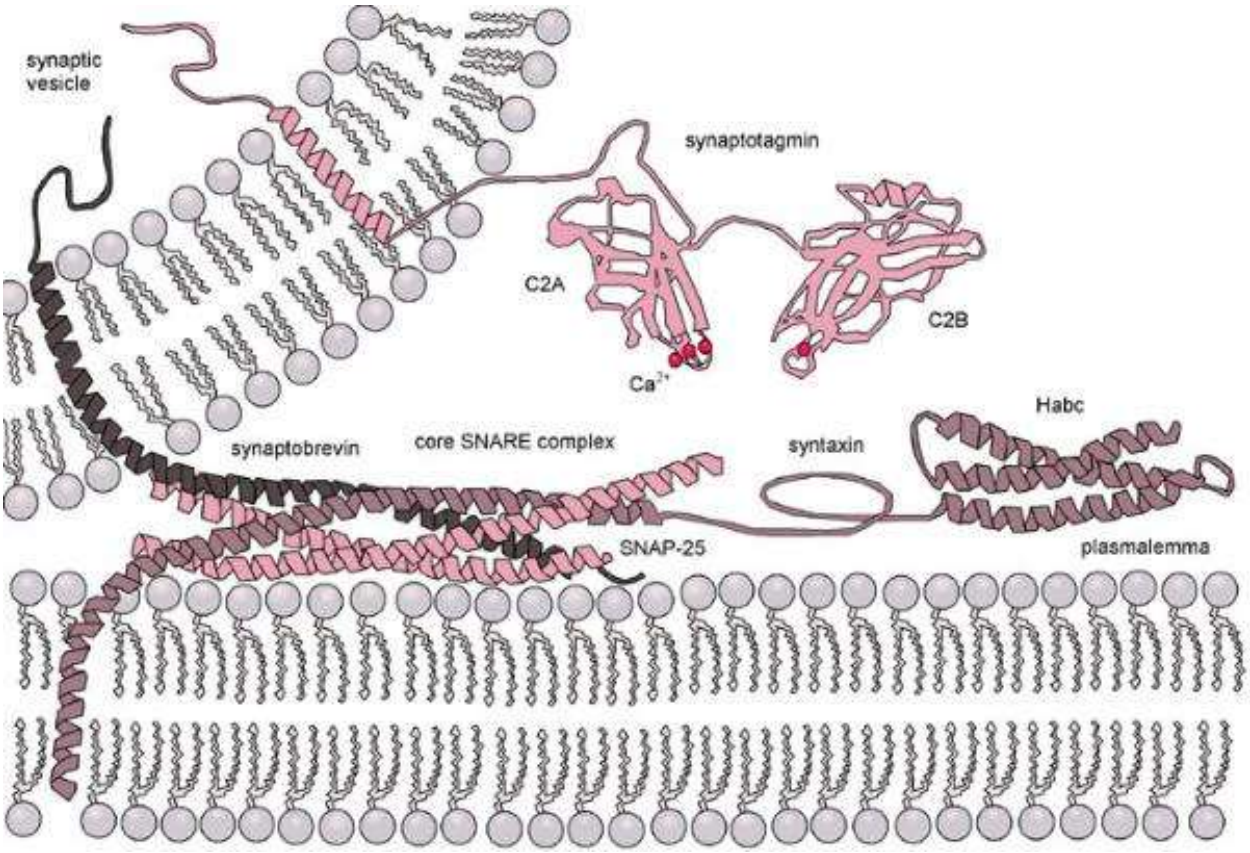


Fig. 15
Overall Membrane Dynamics:

Endocytosis and exocytosis tend to balance the quantity of plasma membrane. More membrane is also made at the Endoplasmic Reticulum with appropriate protein markers. Membrane embedded chemicals are modified during the course of vesicle migration to and from the Golgi apparatus and in various vesicles. Vesicles receive chemical address markers. Some are moved along the microtubule cytoskeleton by molecular motors such as dynein and kinesin. For example vesicles carrying neurotransmitters must migrate long distances to their axon terminals for example from the ventral horns of the spinal column to the muscles of the big toe. In all of these processes membrane dynamics must be closely controlled to maintain the required shape of cells.

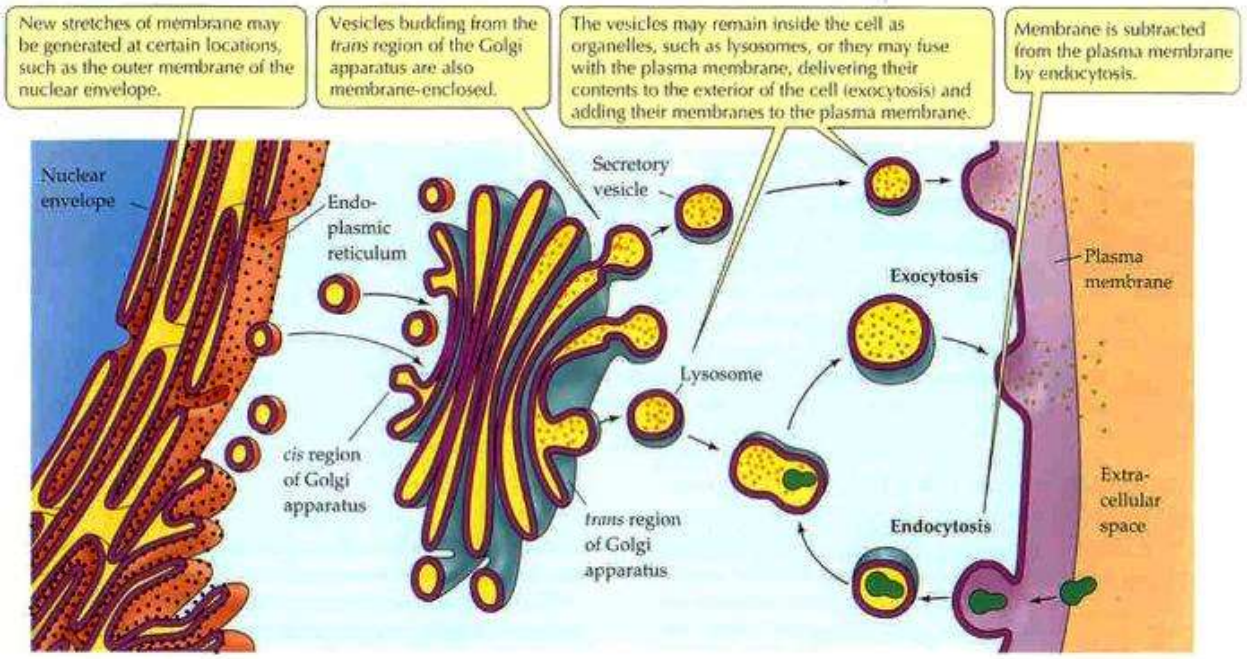


Fig. 16

The Extracellular Matrix:

In animals, extracellular matrix is composed of protein and polysaccharides. It can provide strength, such as cartilage that prevents joints from grinding against each other. It can provide structural support, such as the bone of skeletons. It can help organize cells, such as keeping tendons attached to bones. It can assist with cell signaling and indicate changes in the environment. It can also act as a storehouse to stockpile materials such as proteins, amino acids, sugars and other substances that may be needed by the cell on short notice.

The major proteins found in the extracellular matrix provide adhesion and structure. Adhesion is achieved by the proteins fibronectin and laminin which attach cells to the extracellular matrix. Structure is achieved by the proteins collagen and elastin which allow some body parts to stretch and return to the original shape, such skin and inhaling air into the lungs.

The major polysaccharides in the extracellular matrix are glycosaminoglycans (GAGs) (or proteoglycans). GAGs are very long chains of disaccharides. They tend to be negatively charged and thus get along well with water. As part of the extracellular matrix, they take on a gel-like consistency, which makes them good for uses such as joint fluid and they are also found in the skin and eyes. Proteoglycans may also help to trap and store growth factors and other materials needed in the cell on short notice. In some cells the extracellular matrix is thus like a storage yard.

Collagen is a group of proteins found exclusively in animals, especially in the flesh and connective tissues of mammals. It is the main component of connective tissue, and is the most abundant protein in mammals making up about 25% to 35% of the whole-body protein content. About 30 kinds of collagen have been identified. In the form of elongated fibrils it is mostly found in fibrous tissues such as tendon, ligament and skin. Other forms are abundant in cornea, cartilage, bone, blood vessels, the gut, and inter-vertebral discs.

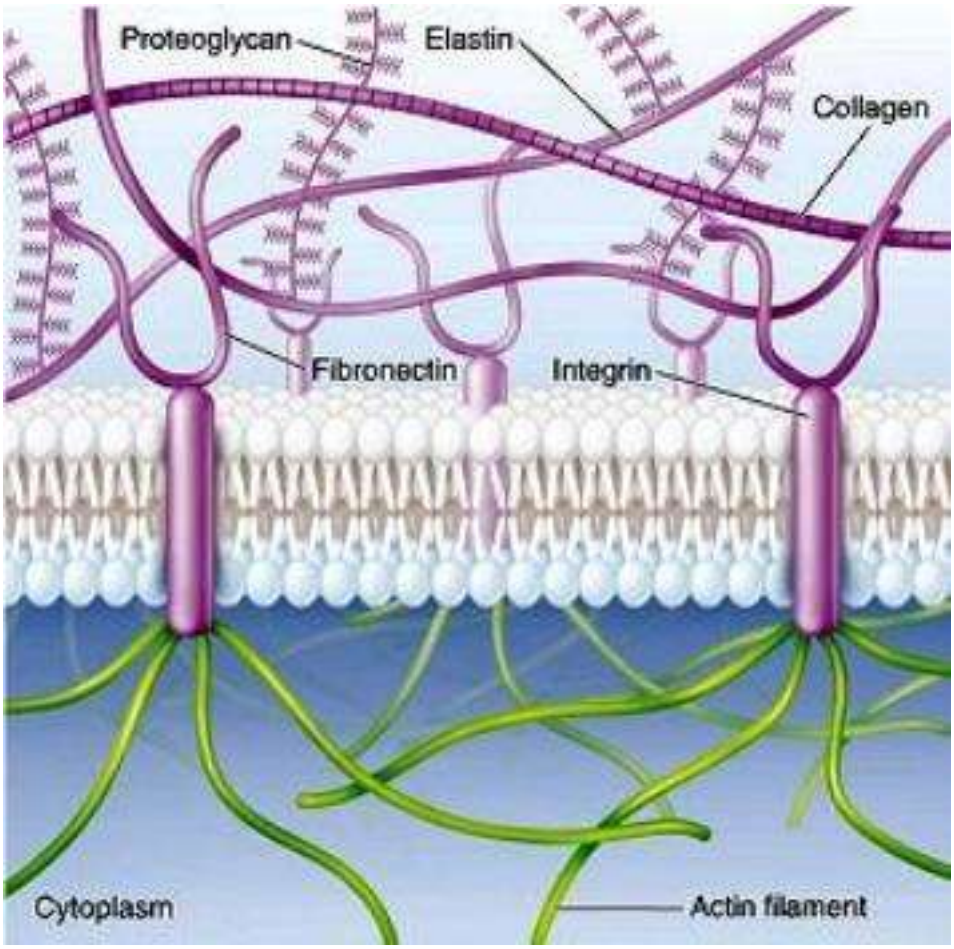

Proteoglycan
Elastin
Collagen
Fibronectin
Integrin
Cytoplasm
Actin filament

Fig. 17

Terms of System 4:

As indicated in the above review cells demonstrate a structural self-similarity to the six domains of any corporation as prescribed by the six Particular Terms of System 4. There are only nine possible ways that four active interfaces (called Centers) can mutually relate with respect to a common inside and outside. Each of these nine ways defines the meaning implicit within each Term. How the Universal Terms integrate the transform sequences of the Particular Terms will be fully dealt with in separate articles but the following chart and definition of the universal hierarchy are common to all.

To summarize, apart from the Sales Term each of the five remaining Particular Terms has both an Expressive (E) and a Regenerative (R) Mode. Since there are three Particular Sets of Terms transforming through the six Term sequence one Step apart, Terms 8, 7 & 4 synchronously alternate with Terms 1, 2 & 5. Some Terms are in the Expressive Mode while others are in the Regenerative Mode. This allows for spanning and integrating events in space and time through three Cycles of transformation. The vertical columns in the Figure 18 chart show the synchronous Terms and their mode (E or R) in the three Particular Sets S1, S2, & S3. Any number of Particular pathways may operate in parallel, for example in any number of cells, or in any number of signaling pathways within each cell.

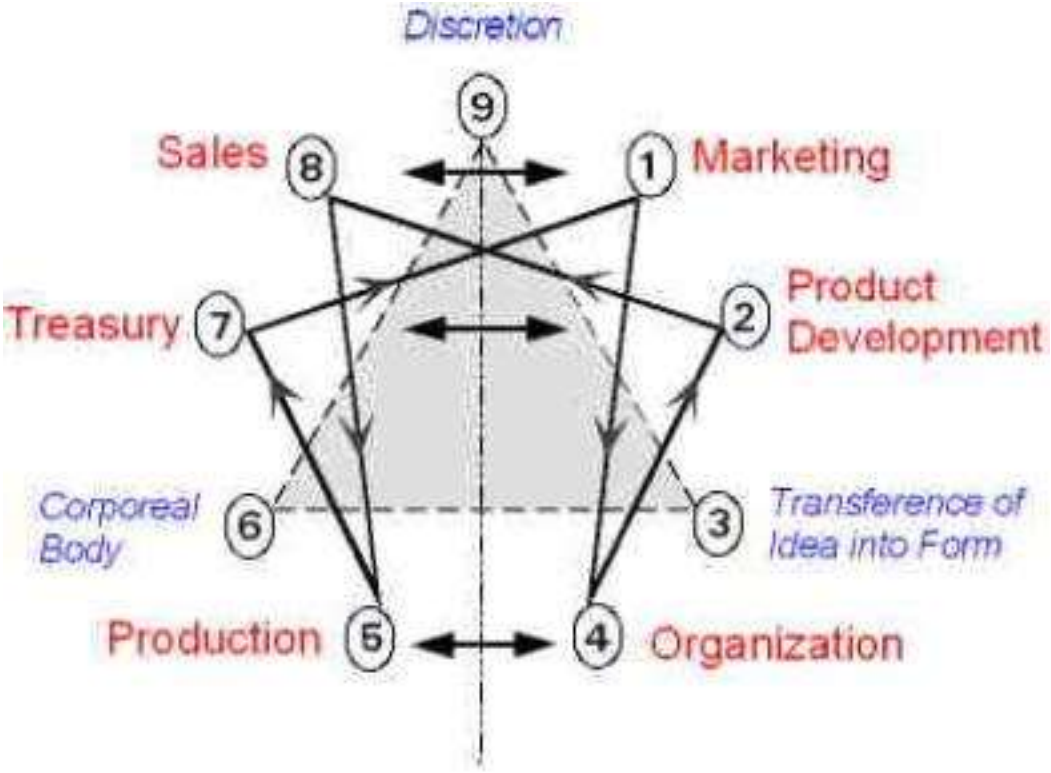
U1 and U2are two Universal Sets each with their own transform sequence. U1 is the Primary Universal Set whereas U2 is the Secondary Universal Set. For example U1 defines the universal hierarchy for all human beings whereas U2 relates to the integration of any specific human being in any given circumstance. The two Universal Sets complete their transform sequences in 4 Steps while the Particular Sets requires 12 Steps as shown in the chart.

The Particular Term numbers 1, 4, 2, 8, 5, 7 (repeating) correspond to the six primary domains of a corporation as illustrated in Figure 19. The analogous functions also occur in a cell. For a detailed diagram of the nine Terms see Figure 31 in the Appendix. The repeating sequence is the inverse of the number 7. Term 7 is the memory term so that recall generates the six Term repeating sequence 1, 4, 2, 8, 5, 7. The sequence is represented in the horizontal rows of Figure 18 chart.

SET	TERM	CYCLE 1				CYCLE 2				CYCLE 3			
U1	Sequence	9	9	8	8	9	9	8	8	9	9	8	8
	Mode	E	E	R	R	E	E	R	R	E	E	R	R
U2	Sequence	3	6	6	2	3	6	6	2	3	6	6	2
	Mode	-	-	-	E	-	-	-	E	-	-	-	E
S1	Sequence	8	5	7	1	4	2	8	5	7	1	4	2
	Mode	E	E	E	E	E	E	E	R	R	R	R	R
S2	Sequence	7	1	4	2	8	5	7	1	4	2	8	5
	Mode	R	R	R	R	E	E	E	E	E	E	E	R
S3	Sequence	4	2	8	5	7	1	4	2	8	5	7	1
	Mode	E	E	E	R	R	R	R	R	E	E	E	E

Fig. 18

In Figure 19 it should be emphasized that Marketing is distinct from Sales. Marketing concerns the forward vision of the organization and its preparedness to meet anticipated market needs and trends. Sales concerns meeting existing market demands with established products. Failure to recognize this distinction is the root cause of the recent financial meltdown. It should also be noted that the Organization Department is usually called the Human Resources or Personnel Department. In a large corporation Human Resources also concerns how the corporation is Organized or structured to operate in response to anticipated Market needs. The corporation must be Organized and manned appropriately. This Organization requires the separate delegation of each of the six primary company departments in order to maintain polar insight into the creative dynamics of the corporation. Organization is not the arbitrary affair that it is often considered to be. It becomes quite complex in large organizations because the same six particular domains break out again within each of the primary departments.



- The Particular Terms of System 4 are shown in red as they apply to a business corporation.
- The flow of work transformation is shown by the connecting lines with arrows. The sequence transformations of the blue Universal Terms are not shown.
- The polar insights into the ***Performance***, ***Potential*** and ***Commitment*** dimensions of the company are shown by the three horizontal arrows respectively. The analogy is useful to understand cell organization and function.

Fig. 19
System 4 Elaboration within itself:

The article *Primary Cilia, the System & Mind* shows how primary cilia are involved with the integration of human Host, Organs and Cells as well as with Host Cell, its internal Organelles and Enzyme Teams. In animal cells with a nucleus this is facilitated by a pair of centrioles at right angles to one another. The basal body of a primary cilium is the mother centriole. It is directed toward the cell exterior such that the primary cilium grows on top of it protruding into the extracellular space to perform its role as an antenna in communication with other cells in organs of the human host. The 9x2 (System 5) microtubule primary cilia structure is subsumed by System 4. System 5 operates like two reciprocating System 4's, one that relates externally to Organs and human Host and one that relates internally to the Organelles and Enzyme Teams within the cell.

The daughter centriole is oriented orthogonally (at 90 degrees) to the mother centriole. It is structured identically (apart from some microfibrils), indicating a self-similar subsuming role in the overall organization of events within the cell. The three Sets of nine microtubules in the daughter centriole are consistent with the three Cycles of System 4 Term transformations, just as they are in the mother centriole.

Diagram of a Centriole:

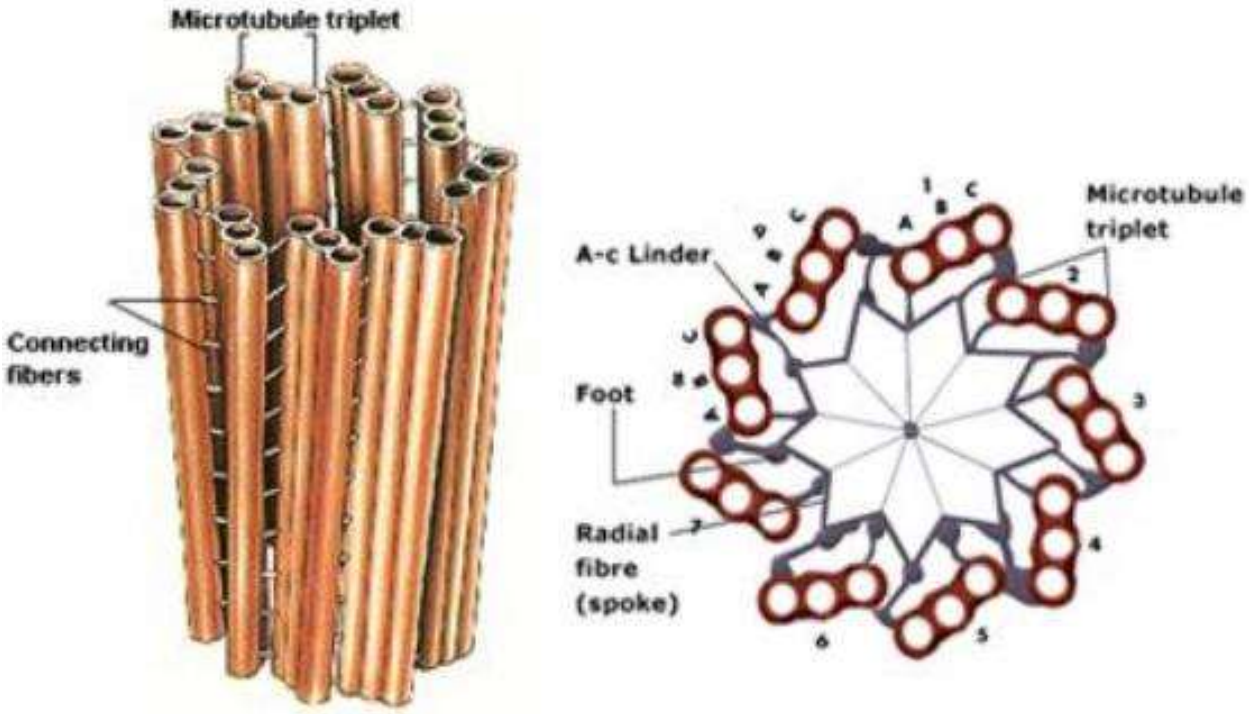


Fig. 20

In System 4 there is a demonstrated intimate triadic relationship between a **Host human being (C1),** their **Organs (C2)** and **Cells (C3)** within the open **molecular interface (C4)** of Term 6 as in Figure 21. This overall triad for a complete human being subsumes a self-similar intimate triadic relationship between the **Host Cell type (C1)** in each organ tissue, its **Organelles (C2)**, and its complement of **Enzymes (C3)** that catalyze changes in the open **molecular interface (C4)** common to all molecular processes everywhere. The human **Host-Organ-Cell** triad thus subsumes the **Cell-Organelle-Enzyme** triad through the related organizing agency of the orthogonal mother and daughter centrioles.

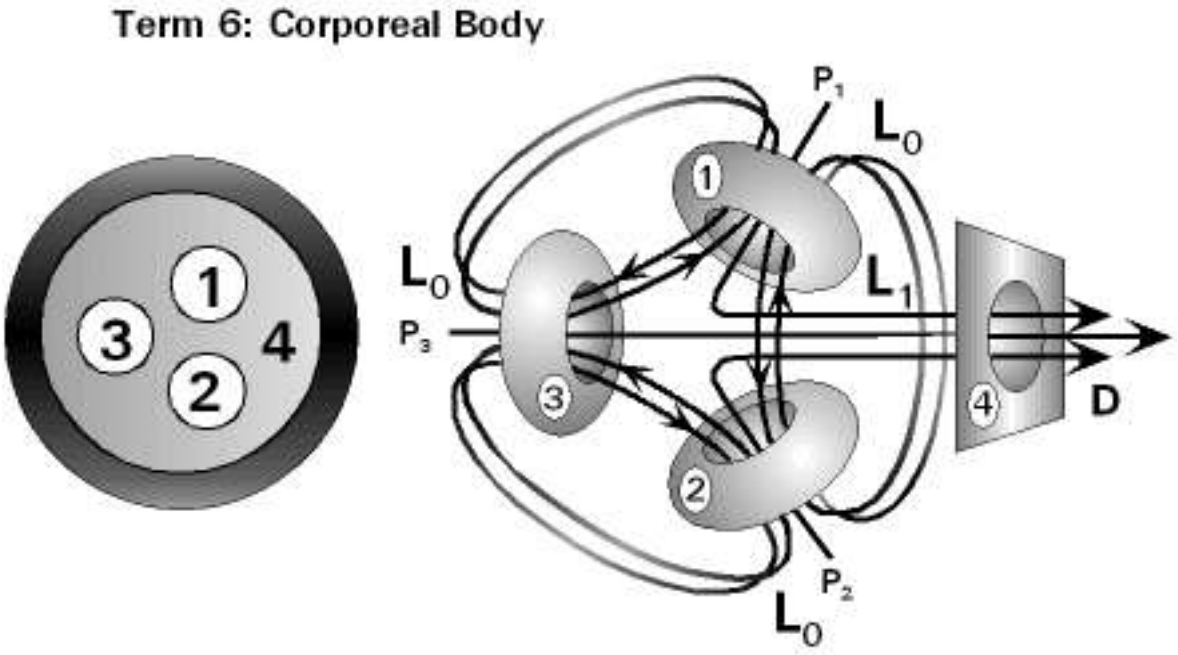


Figure 31

Fig. 21

Term 1E (Expressive Mode):
T1E represents the perception of immediate market needs and the current capacity of the cell to meet those immediate needs. In a business organization this is consistent with having the organized productive capacity up and running to maintain the flow of available products to customers as orders come in. In a cell it concerns the current electronic organization of the cell, including the membrane and its receptors, to respond to the current pattern of external needs.

Note that Term T1E has a perceptual axis that that relates the subjective internal aspects of the organization, in this case a cell, to the objective outside environment. The perceptual axis of the cell corresponds with the center of the bi-lipid membrane that has negatively charged heads inside and out, together with high concentrations of positively charged sodium and calcium ions outside the cell membrane. In this way the perceptual axis of the cell membrane actively relates outside to inside and vice versa. The white arrows in Figure 22 designate coalescence across the membrane between inside to outside. This coalescence encompasses all trans-membrane signaling processes, active transport mechanisms, ion channels, and diffusion. These factors involve concentration gradients associated with electronic patterns. The alignment of the coalesced pairs of active interfaces (called Centers) with respect to the inside and outside of the cell is very significant.

Term 1E: Perception of Need

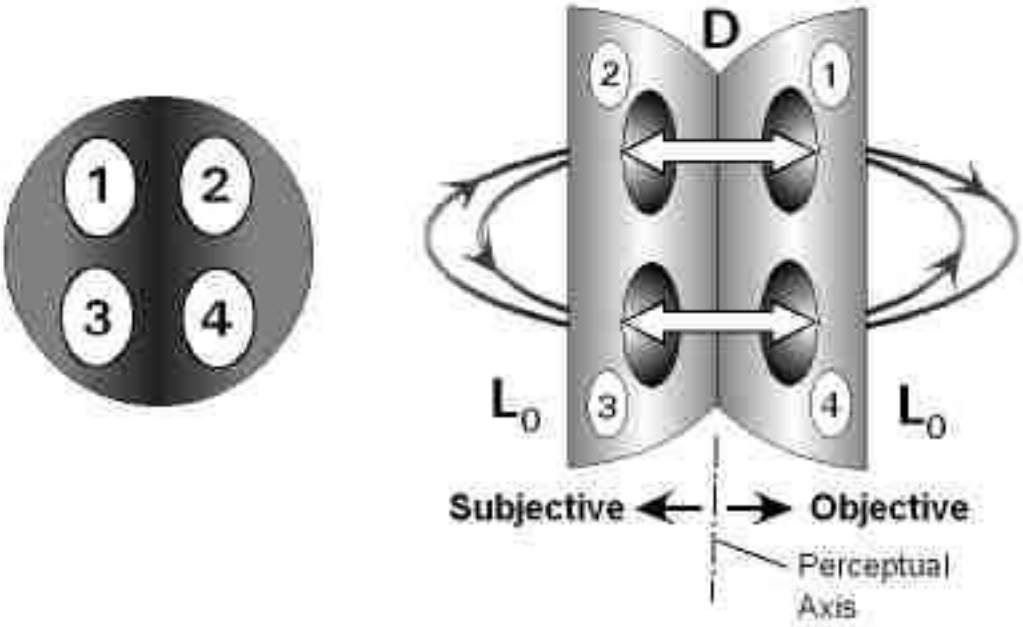


Fig. 22

The diagram illustrates the integrating ***Idea*** of the cell **(C1)** as **Patterned Energy (PE)** aligned with **Molecular Form (C4)** outside the cell membrane. This indicates the external electronic pattern **(C1)** of the membrane and the extracellular matrix including signal receptors and ion concentrations is aligned with **C4** which represents the molecular environment including the molecular form of the cell. The cell membrane is itself a complex organelle that defines the cell boundary and actively responds to the environment inside and outside.

The cell **Idea (PE- C1)** is *coalesced* with **Organelle Knowledge (OK- C2)** across the membrane. This integrates the **Idea (C1)** of the cell with **Knowledge (C2)** through established membrane processes such as signaling across the membrane and transport mechanisms that also relate to other organelles subsumed within the cell. The coalescence indicates that they work together to bridge the membrane. The **Organelle Knowledge (C2)** interface is subjectively aligned inside the cell with the **Routine (C3)** interface that constitutes **Enzyme Teams (ET)** of chemical processes within the cell.

The enzyme team **Routine** interface **(C3)** is coalesced with molecular **Form (C4)** to act as a bridge across the cell membrane just as the C1=C2 coalescence acts as a bridge across the cell membrane. The C3=C4 coalescence represents specific patterns of enzyme catalyzed chemical processes that have occurred in the past. It thus represents elements of technique that the cell is **Known (C2)** to be capable of as integrating patterned **Ideas (C1)**. These C3=C4 elements of technique are the **expressive core** of the memory term T7E, that immediately precedes and transforms into term T1E in the same Particular Set transform sequence. By examining the Figure 18 chart below it can be seen that in Cycle 1 this transform sequence from T7E to T1E is in Set 1. (See the **memory core** coalescence **C3=C4** of Term T7R in Figure 26 below.)

T1E initiates signaling processes that lead to Production of products for export from the cell, such as vesicles containing enzymes and signal transmitters in neurons and sperm cells. These are generally produced, processed and packaged in the ER and Golgi apparatus, however the smooth ER pathway may also be used for some cell maintenance in most cells. For instance the rough endoplasmic reticulum synthesizes proteins, while the smooth endoplasmic reticulum synthesizes lipids and steroids, metabolizes carbohydrates and steroids, and helps regulate calcium concentration, drug detoxification, and attachment of receptors on new cell membrane proteins.

Three Interdependent Particular Set Transformations:
Because there are three Particular Sets of active interfaces transforming through the six Term transform sequence one step apart Terms 1, 2, 5 alternate with Terms 8, 7, 4 in each parallel pathway. In Step 2 of each 4 Step Cycle T1R is synchronous with T2E and T5E. In Step 4 of each 4 Step cycle T1E of is synchronous with T2R and T5R. The chart in Figure 18 is repeated below. It lists synchronous Sets of Terms in the vertical columns and transformation sequence Steps in horizontal rows.

In Step 4 of Cycle 1 the expressive Term T1E of Set 1 as described above is thus organized to receive patterned input from outside consistent with its synchronous terms T2R and T5R. This means that T1E representing the expressive capacity of the cell is consistent with the regenerative Creative Ideas T2R of Set 2 and the regenerative Production of molecular needs T5R in Set 3. This primes the ability of the cell to receive signaled input from outside consistent with its patterned capacity to respond as it has in the past. This may happen in any number of parallel signaling pathways of the same kind.

In Step 2 of each Cycle T1R is synchronous with T2E and T5E in different Sets. Centers 1 and 2 exchange places from that above in T1E and the regenerative Perception of Need term T1R switches to internal maintenance concerns. The cells internal needs are related to expressive conditions associated with a new Creation of Idea T2E and Production of proteins T5E for export. The T2E term derives from the signaling input from outside the cell in the T4E term that preceded it in the transform sequence of the same Set as shown in the Figure 18 chart. There is thus a continuous flux of changing needs between cells throughout the body according to activities of the Host human being. The Production T5E term derives from the preceding Sales term T8E in the transform sequence of the same Set that balances an appropriate response to external signaling input. There is more on this in other articles.

In this article we are only dealing with two Steps involving the transformation from Term 1E to Term 4E and Term 1 R to Term 4R. These two steps concern membrane and signaling processes as they relate to expressive export form the cell and regenerative internal cell needs. Other Steps are reviewed in other articles. The Particular Steps are integrated and regulated by the Universal Sets into three 4 Step Cycles. The interdependent transform sequences of the Universal Sets will also be reviewed in separate articles. They are partially reviewed in the article Primary Cilia, the System & Mind.

Term 1R (Regenerative Mode):
In the regenerative mode T1R, C1 and C2 have exchanged places. Now organelle **Knowledge** (C2) is coalesced from outside across the membrane with the electronic patterned cell **Idea** (C1) inside the membrane. The integrating energy pattern (EP) or cell **Idea** (C1) is now aligned with subjective Enzyme Team **Routines** (C3). The latter are coalesced across the membrane with molecular **Forms** (C4). The coalescence (C3=C4) is an element of technique in each pathway different from that in T1E above. The coalescence derives from the regenerative core of memory in the memory term T7R in the previous transform Step of the same Particular Set. Term T7R is illustrated in Figure 26.

In a business organization Term 1R concerns identifying regenerative needs as they relate subjectively to upgrading the company infrastructure, its methods and related equipment to meet future perceived needs and trends in the Market environment. In a cell the infrastructure is maintained by chemical synthesis according to the assessment of subjective needs. This is accommodated by C1 and C2 exchanging places from that in Figure 22 to that in Figure 23.

SET	TERM	CYCLE 1				CYCLE 2				CYCLE 3			
U1	Sequence	9	9	8	8	9	9	8	8	9	9	8	8
	Mode	E	E	R	R	E	E	R	R	E	E	R	R
U2	Sequence	3	6	6	2	3	6	6	2	3	6	6	2
	Mode	-	-	-	E	-	-	-	E	-	-	-	E
S1	Sequence	8	5	7	1	4	2	8	5	7	1	4	2
	Mode	E	E	E	E	E	E	E	R	R	R	R	R
S2	Sequence	7	1	4	2	8	5	7	1	4	2	8	5
	Mode	R	R	R	R	E	E	E	E	E	E	E	R
S3	Sequence	4	2	8	5	7	1	4	2	8	5	7	1
	Mode	E	E	E	R	R	R	R	R	E	E	E	E

Fig. 18

Term 1R: Perception of Need

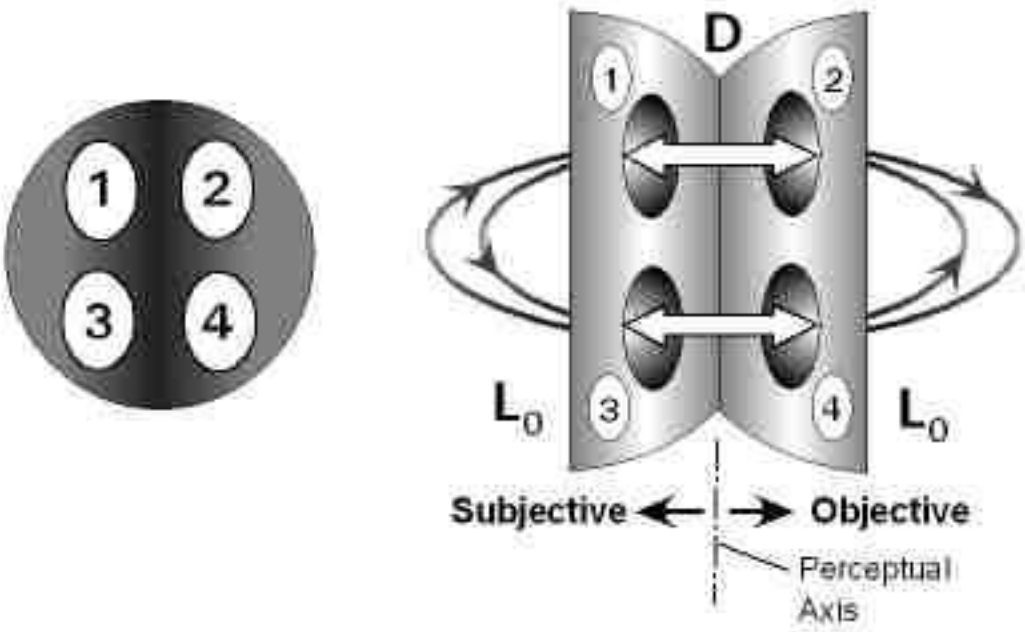


Fig. 23

Degenerate Variants of Term 1:
If Centers 3 and 4 exchange places this initiates a degenerate involutionary variant in the sequence of transformations that follows related to that Particular Set in that pathway. In the cell this is associated with decay processes and disease. The Routines of the cell represented by C3 of the Set do not relate to the cell environment in a subjective to objective way, but vice versa. Values become inverted. Routines such as cell replication become executed for their own sake as in tumors and cancers. The cell develops as a tumor or decays as an entity sufficient unto itself, even though the coalesced Centers C3=C4 still represent the same recalled element of technique but reversed with respect to inside and outside. This can have many diverse consequences depending on the related intimate function of the coalesced Centers 1 and 2. There is both an expressive and a regenerative mode for the involutionary variant that also allows involutionary energies to be redeemed. For purposes here we will assume that Centers 3 and 4 do not exchange places and focus on the evolutionary variant.

Signaling Cascades:

Internal biochemical signaling cascades are distinct from what happens at the membrane. The exposed internal end of the embedded protein has components that require activation by adjacent membrane proteins such as ATP, GTP, and enzymes that act together at the membrane prior to initiating the cascade through a chain of phosphorylation. The cascade can also be inhibited analogous to the way a neuron can be inhibited. Many parallel signaling pathways are possible analogous to different nerve pathways that sense heat, or vibration, or fine touch, or pain, or body position, or four kinds of taste nerves, and so on. In a cell the possible membrane processes and signaling cascades are far more complex and numerous.

Signaling cascade needs are identified by Term 1 but the cascades themselves are represented by Term 4. The two alternating expressive and regenerative modes are T4E and T4R.

T4E (Expressive Mode):
Note how term T4E is configured in Figure 24. Organelle Knowledge C2 is coalesced with the cell Idea C1 as an integrated energy pattern that embraces all organelles including the cell membrane. C1 and C2 each relates through the other to simultaneously represent the cell through its various enzyme Routines (C3) as they objectively relate to molecular Forms (C4). This is an integrated relationship that in System 4 is called a Relational Whole and designated as R. Thus we have R2 and R3 simultaneously relating energy patterns, organelles and enzymes in a fully integrated objective relationship to molecular Forms.

Countercurrent to the simultaneously integrated R2 and R3 a signaling cascade is represented by R1. The signaling messenger (or ligand) in this case comes from outside the cell and docks on the external receptor terminal of integral protein receptors. Docking of the ligand changes the physical shape of the receptor triggering the enzymes inside the cell membrane to initiate the cascade to organelles, mainly to the nucleus. The cascade depends upon a series of kinase enzymes that phosphorylate successive steps in the cascade network. Phosphate groups are negatively charged so the step by step cascade is analogous to electronic signal transmission from neuron to neuron across synaptic junctions.

Term 4E: Sensory Organization

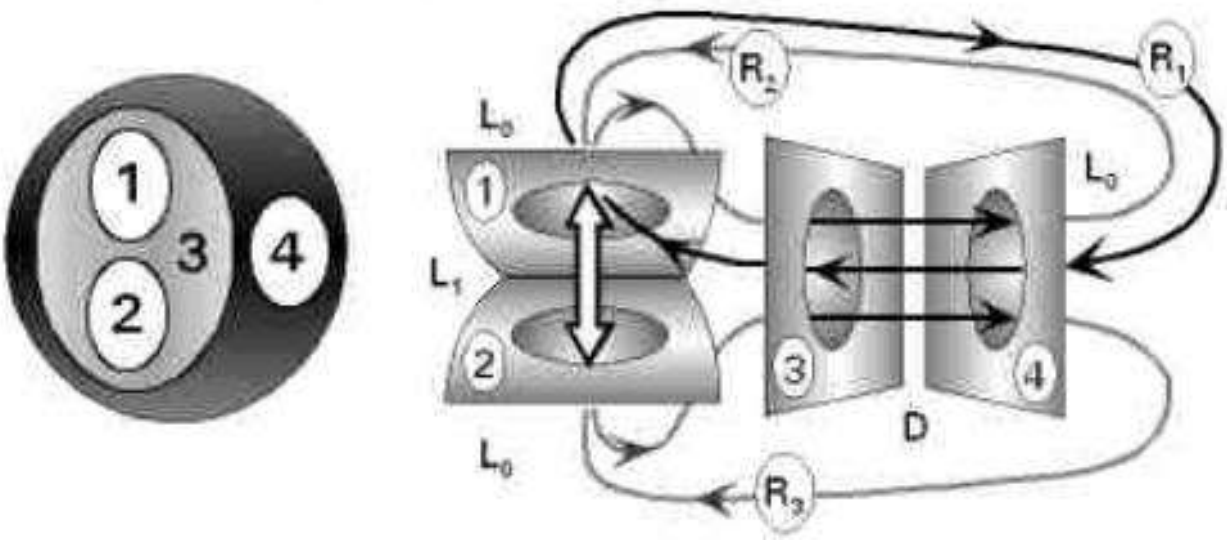


Fig. 24

Sensory cells in the body, such as nerve endings, auditory and vestibular hair cells, retinal cells, and so on respond to external physical input that results in signal transmission via vesicles that discharge their contents into synapses. Receptors on nerve cells across the synapse relay the signal on. The electrical signal opens voltage gated calcium channels. The rapid flow of calcium ions into the axon ending from outside stimulates the discharge of neurotransmitters into the synaptic cleft. Receptors on the opposite side of the synaptic gap bind neurotransmitter molecules which can directly open ligand gated ion channels changing the local transmembrane potential which generally excites the neuron across the synapse to fire.

In the nervous system and muscles signal transmission from cell to cell depends upon ion transport. Within the cell complex signal transduction networks depend on kinase enzymes that phosphorylate (exchange negatively charged phosphate ions) in successive chemical steps. Both nerve signals and cell signalling thus involve a succession of electronic events.

The signaling cascade initiated by a molecular signal C4 is transmitted through kinase enzymes (C3) that complete the Relational Whole R1 in electronic energy patterns C1. When the cascade terminates on transcription factors in the nucleus it initiates gene expression when T4E transforms to T2E. Note from the Figure 18 chart that T4E is synchronous with T8E in another Set that balances signaling input with an appropriate response pattern and T7R in a third Set that recalls a regenerative sequence to replenish cell needs. All three Sets are synchronously at work in each pathway. There may be many parallel pathways.

T4R (Regenerative Mode):
The regenerative mode of the sensory Organization Term T4R derives from the T1R term that immediately precedes it in the transform sequence. C1 and C2 have exchanged places from that in Figure 24 to that in Figure 25. The Relational Whole R1 completes its circuit not through electronic energy (Idea) processes C1 but through organelle Knowledge processes (C2) of the cell. Generally this involves the release of calcium stores from organelles, especially the Endoplasmic Reticulum which has a widespread effect on signaling, gene transcription, protein synthesis to the cytosol as well as processes within the ER. There are related events in the nucleus and mitochondria. These events focus on regenerative needs.

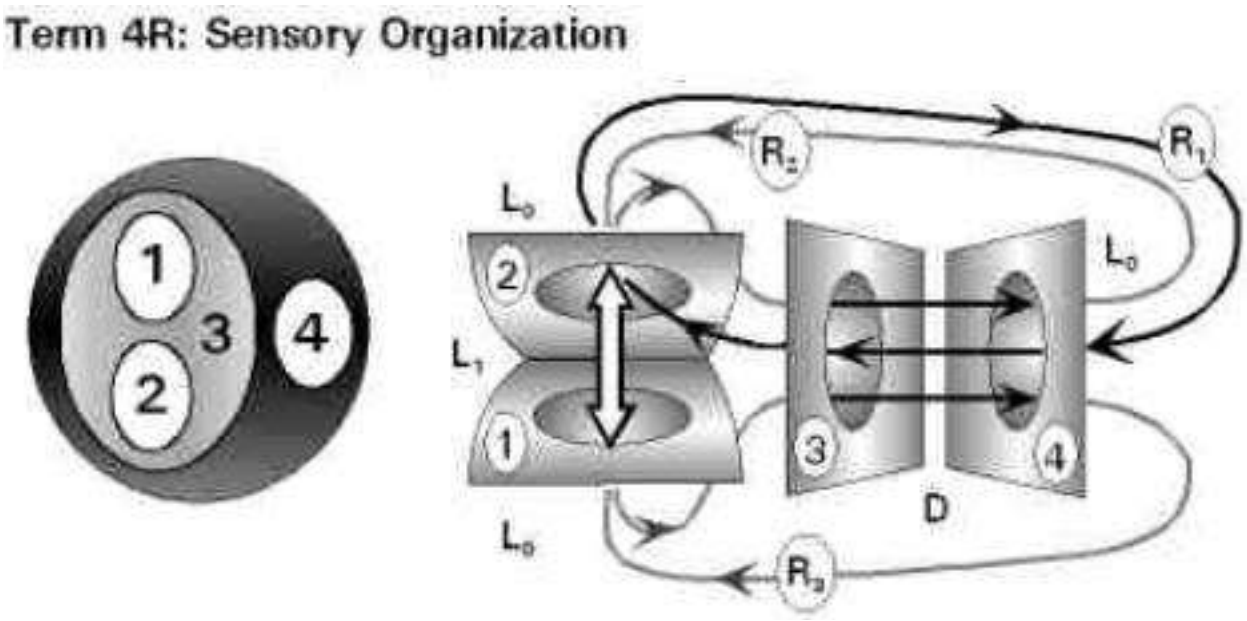


Fig. 25
Inositol triphosphate (IP3) is an important second messenger that docks on calcium transport channels in the Endoplasmic Reticulum, opening them and rapidly releasing calcium stores into the cytosol as shown simplified in Figure 4. This initiates a broad range of signaling events. The complexity of the process is fully described under the first Appendix heading.

The IP3 signal to the ER generates complex cytoplasmic Ca2+ concentration signals including propagating waves. In addition there are channels activated by cADPR (cyclic ADP-ribose), Sphingosine and a distinct Ca2+ release pathway activated by NAADP (Nicotinic Acid Adenine Dinucleotide Phosphate). Within Ca2+ storing organelles, Ca2+ ions are bound to specialized Ca2+ buffering proteins. These include CS (Calsequestrins), CR (Calreticulins) and CN (Calnexins). In the cytosol, there are mobile Ca2+ buffers; the CB (Calbindins), PV (Paravalbumin), Calm (Calmodulin) and S100 protein families that blunt Ca2+ spikes and assist in redistribution of Ca2+ ions. The Ca2+ release from internal stores occurs through channels formed by IP3 Receptors. Ca2+ release activates Calm (Calmodulin) which further activates Caln (Calcineurin), CamKKs and CamKs (CamK4 and CamK2). Caln facilitates NFAT (Nuclear Factor of Activated T-Cells) translocation to the nucleus, a process essential for axonal growth. CamK4 and CamK2 phosphorylates CBP (CREB Binding Protein) and Histone Deacetylases, HDAC4, HDAC5 and HDAC7, which mediates some nuclear Ca2+ signals. HDAC export allows MEF2 (Myocyte Enhancing Factor-2) to activate transcription by recruiting other Ca2+ sensitive transcriptional factors such as NFAT (Nuclear Factor of Activated T-Cells) and transcriptional coactivators such as p300. CREB (cAMP Response Element-Binding Protein) can be phosphorylated by CamK4 at a number of sites other than Ser133, including Ser129, Ser142 and Ser143. Phosphorylation of Ser142 and dephosphorylation of Ser133 residue by CamK represses CREB activity and thus gene transcription.

By following the route of R1 in Figure 25 it can be seen that these complex signaling processes initiated by the Form of a molecular signal C4 are orchestrated through enzyme Routines C3 as they relate to organelle Knowledge C2, especially the Endoplasmic Reticulum. Organelle Knowledge C2 is coalesced with the integrating electronic Idea pattern C1 as evidenced by the rapid release of calcium ion stores into the cytosol. The C1=C2 coalescence consequently can have many regenerative consequences related to such events as cell division, cell proliferation, fertilization, development, and related behavior, memory and learning. Keep in mind that the C1=C2 coalescence means that R2 and R3 simultaneously relate enzyme teams C3 to molecular signaling processes C4.

The IP3 pathways are represented in the more comprehensive diagram and description given in the Appendix. Note from the Figure 18 chart that T4R that signals regenerative responses is synchronous with T8E which balances signaling input with appropriate response patterns and T7E which recalls an expressive sequence which will draw on the regenerated cell's resources.

Sensory Input Tensionally Coupled to Recall:

We know that the recall process is coupled to sensory input. We see a familiar face and say hello. We recognize them; you might say re-cognize. We look at old photos and a flood of memories come back. If it did not work that way our responses could not relate to ongoing circumstances. We might be called absent minded or in extreme cases committed to a psychiatric facility or care home. We know that it works that way in the nervous system and System 4 requires that it also works that way in the cell.

Term 7R: Memory Resources

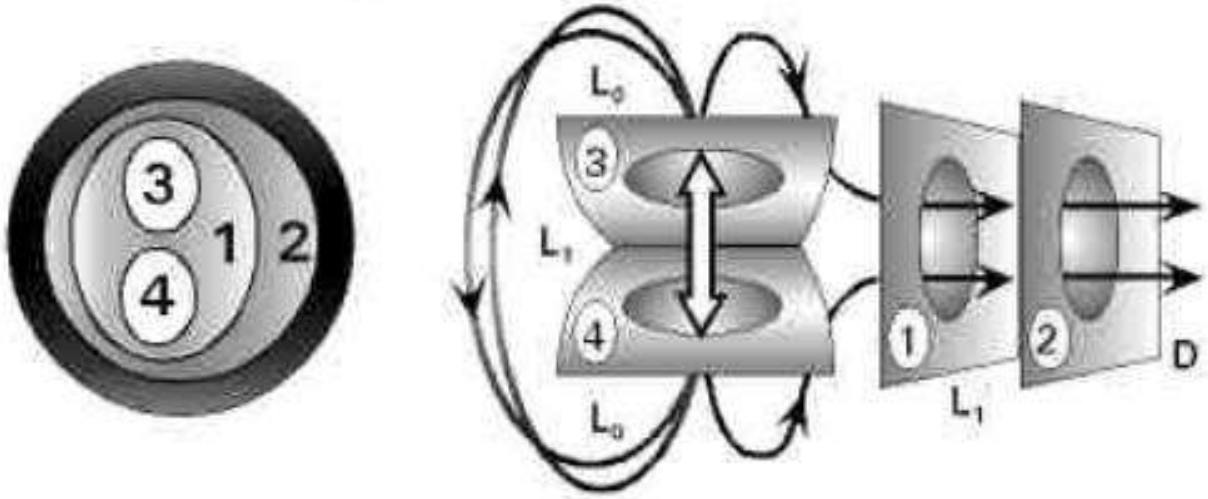


Fig. 26
Appendix:

Inositol Triphosphate Signaling: (A complex process)

IP3 (Inositol 1,4,5-triphosphate), also known as a second messenger, is a molecule that functions to transfer a chemical signal received by the cell, such as from a hormone, neurotransmitters, growth factors and hypertrophic stimuli such as AngII (Angiotensin-II), Beta-adrenergic receptor agonists, and ET1 (Endothelin-1) to various signaling networks within the cell. IP3 is known to play a crucial role in initiating and propagating these messages; however, the precise mechanism of how IP3 relates to the next element in its signaling pathway, the calcium wave, remains highly controversial. The receptors for IP3, IP3R (IP3 Receptor) constitute a family of Ca2+ channels responsible for the mobilization of intracellular Ca2+ stores. Three different receptor types have been molecularly cloned, and their genes have been classified into a family. IP3Rs are tetramers that act as ligand-gated channels facilitating Ca2+ release from internal stores/endoplasmic reticulum. The primary structure of the IP3R contains 3 domains: an Inositol triphosphate binding domain near the N terminus, a coupling domain in the middle of the molecule, and a transmembrane spanning domain near the C terminus (Ref.1). See Figure 27.

Two essential signaling pathways involve the intracellular generation of Inositol Phosphates. The first signaling pathway is initiated by PLC (Phospholipase-C). PLC's are soluble proteins that are partly cytosolic and partly associated with membrane. Based on their functional and structural characteristics, they have been grouped into four classes: PLC-Delta, -Beta, -Gamma and -Epsilon. Hormones and neurotransmitters bind to GPCR (G-Protein Coupled Receptors) and both the heterotrimeric G-AlphaQ/11 and G-Beta Gamma subunits regulate the function of PLC-Beta. Other members of the PLC family are activated by growth factors that activate RTK (Receptor Tyrosine Kinases). Most growth factors that signal through RTKs stimulate Ras by recruiting the GEF (Guanine-Nucleotide Exchange Factor) SOS (Son of Sevenless) to the membrane. SOS exists in a complex with the adapter protein GRB2 (Growth Factor Receptor-Bound Protein-2) and SHC.

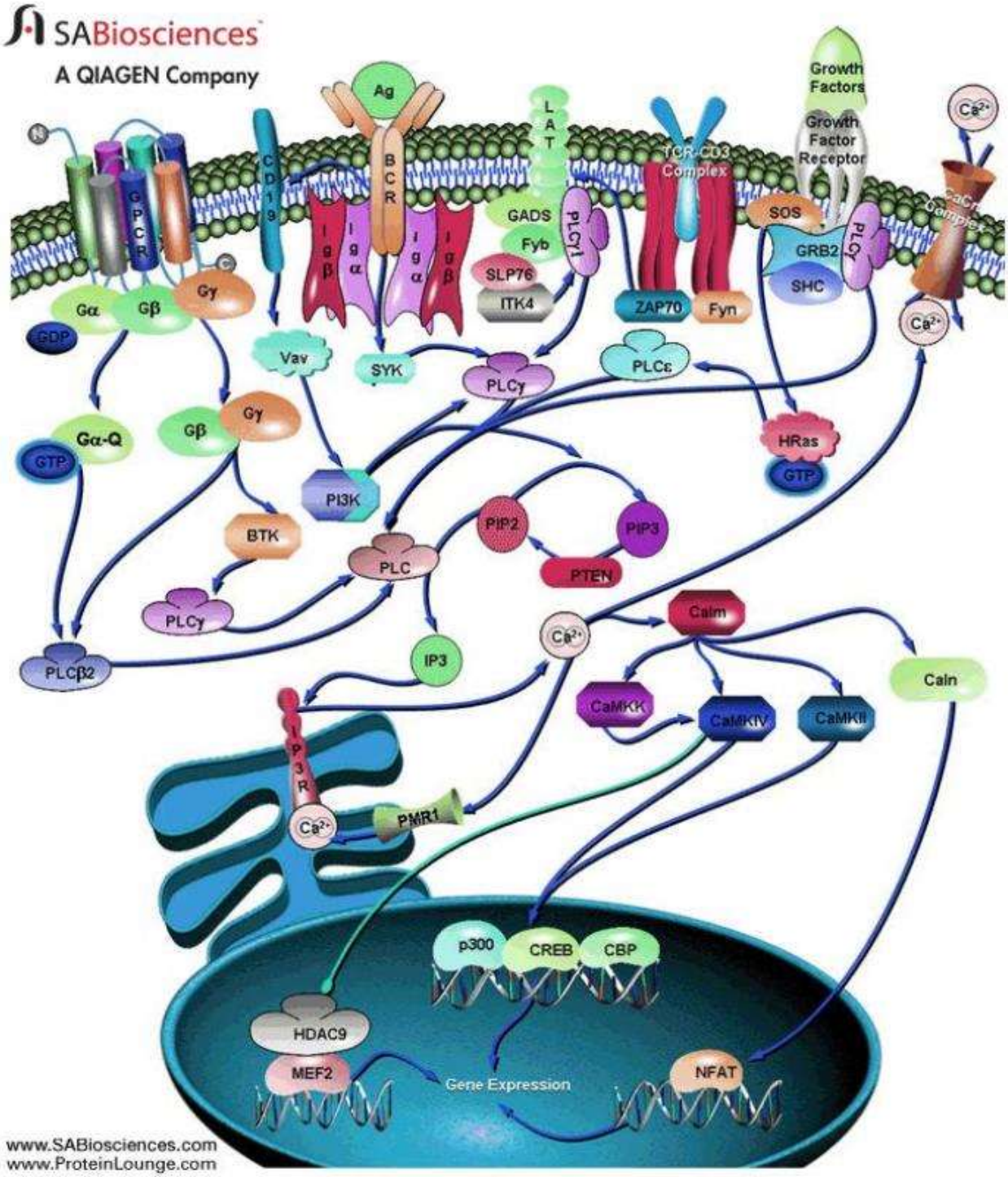

SABiosciences
A QIAGEN Company
Ag
BCR
CD19
LAT
GADS
Fyb
SLP76
ITK4
PLCγ1
TCR-CD3 Complex
ZAP70
Fyn
Growth Factors
Growth Factor Receptor
SOS
GRB2
SHC
PLCγ
GPCR
Gα
Gβ
Gγ
GDP
Vav
SYK
PLCγ
PLCε
Gα-Q
GTP
HRas
GTP
PI3K
BTK
PLC
PIP2
PIP3
PTEN
PLCγ
PLCβ2
IP3
Ca2+
Calm
Caln
CaMKK
CaMKIV
CaMKII
IP3R
Ca2+
PMR1
p300
CREB
CBP
HDAC9
MEF2
Gene Expression
NFAT
www.SABiosciences.com
www.ProteinLounge.com

Fig. 27

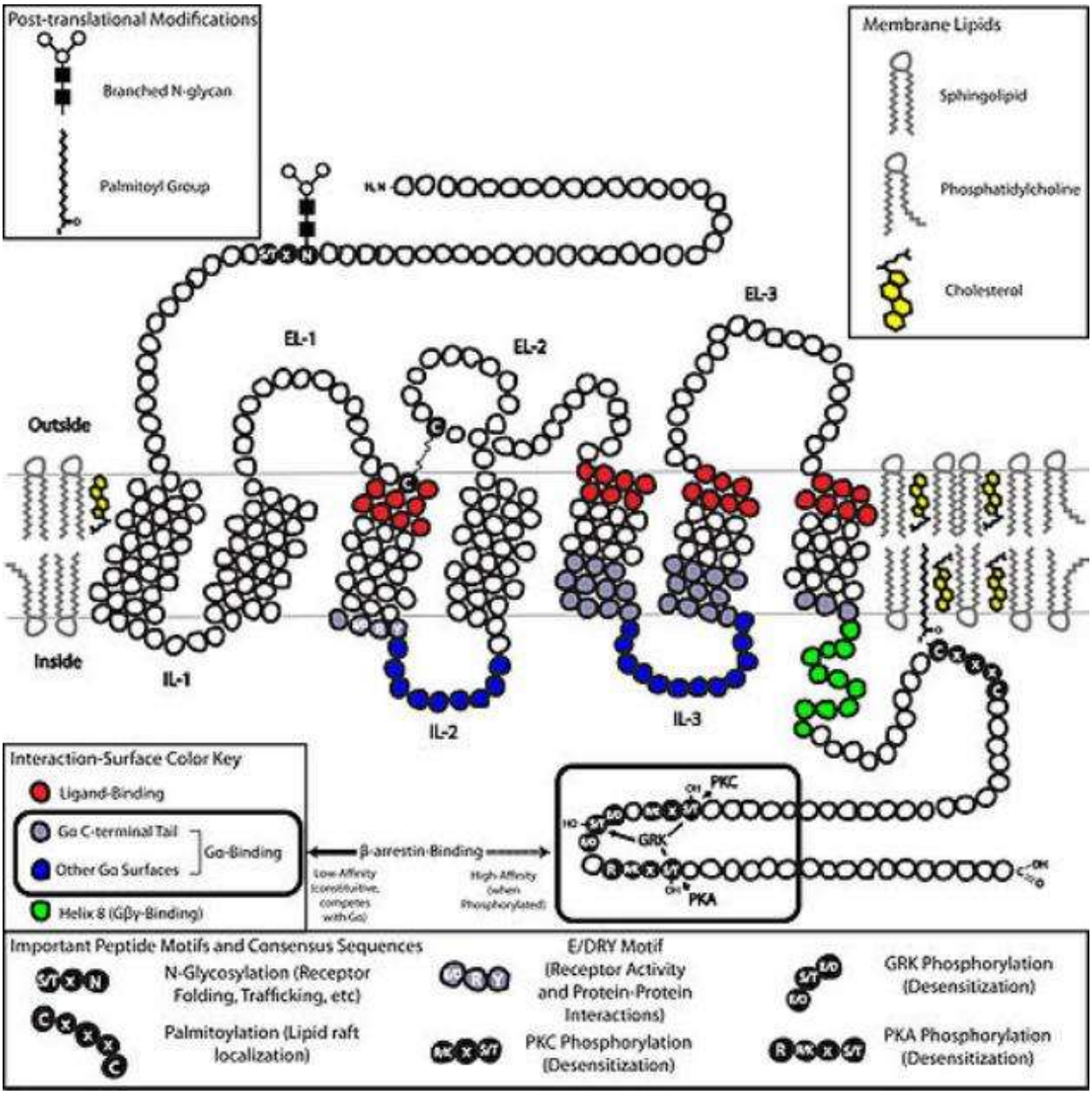

Post-translational Modifications
Branched N-glycan
Palmitoyl Group
Membrane Lipids
Sphingolipid
Phosphatidylcholine
Cholesterol
EL-1
EL-2
EL-3
Outside
Inside
IL-1
IL-2
IL-3
Interaction-Surface Color Key
Ligand-Binding
Gα C-terminal Tail
Other Gα Surfaces
Gα-Binding
Helix 8 (Gβγ-Binding)
β-arrestin-Binding
Low Affinity (constitutive, competes with Gα)
High Affinity (when Phosphorylated)
PKC
GRK
PKA
Important Peptide Motifs and Consensus Sequences
N-Glycosylation (Receptor Folding, Trafficking, etc)
Palmitoylation (Lipid raft localization)
E/DRY Motif (Receptor Activity and Protein-Protein Interactions)
PKC Phosphorylation (Desensitization)
GRK Phosphorylation (Desensitization)
PKA Phosphorylation (Desensitization)

Fig. 28

Figure 28 illustrates the GPCR Conformational Activation. Ligand binding disrupts an ionic lock between the E/DRY motif of TM-3 and acidic residues of TM-6. As a result the GPCR reorganizes to allow activation of G-alpha proteins. The side perspective is a view from above and to the side of the GPCR as it is set in the plasma membrane (the membrane lipids have been omitted for clarity). The intracellular perspective shows the view looking up at the plasma membrane from inside the cell.

Abbreviations, etc:
GPCR domains:
IL-1 to IL-3= Intracellular loops 1-3
EL-1 to EL-3= Extracellular loops 1-3

Other:
G-alpha= Alpha subunit of a heterotrimeric G-protein
G-beta/gamma= G-beta/gamma heterodimer of heterotrimeric G-protein
The figure is based on information found in the review article "The Year In G Protein-Coupled Receptor Research" Molecular Endocrinology 24 (1): 261-274. (2010)

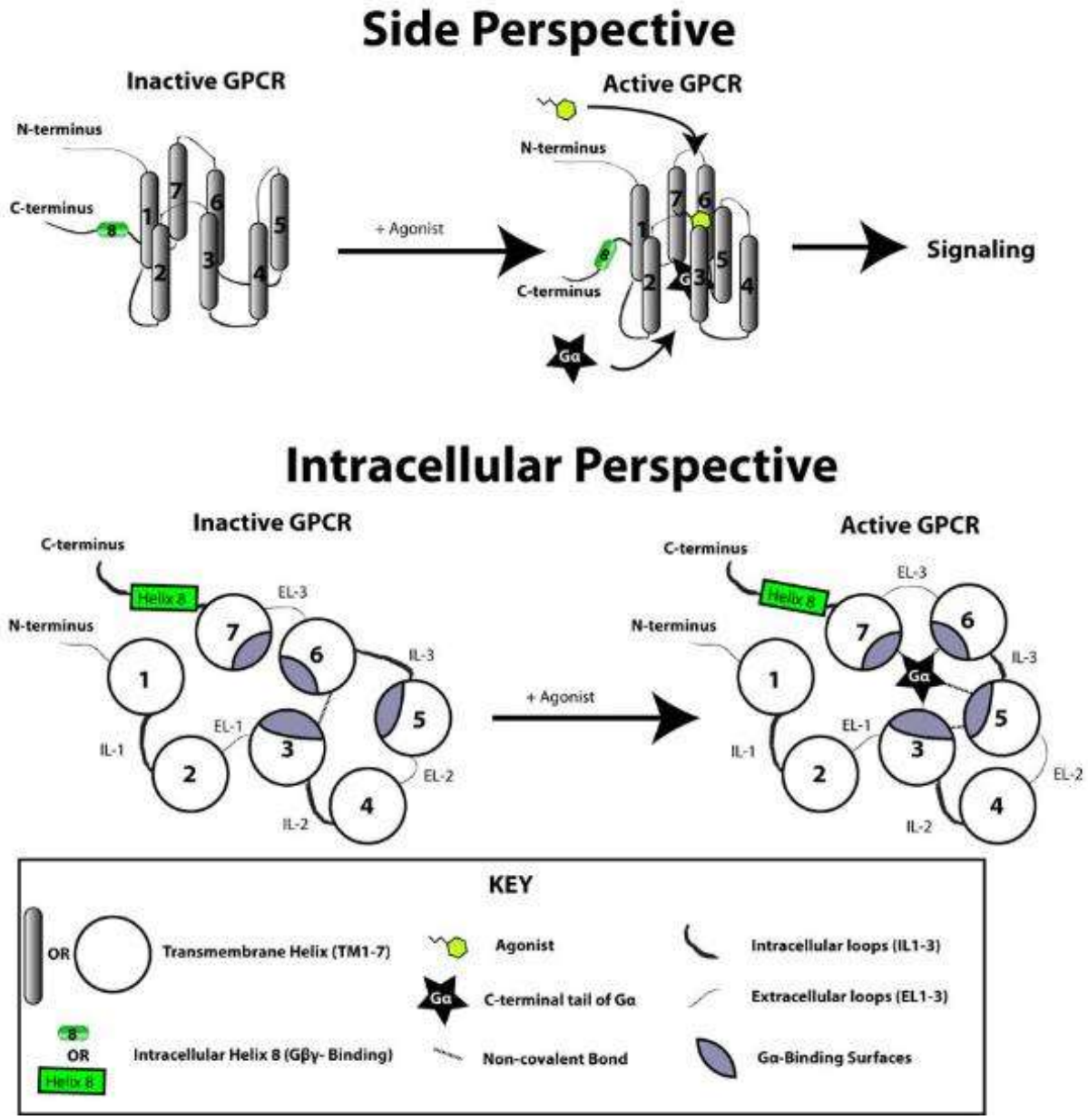
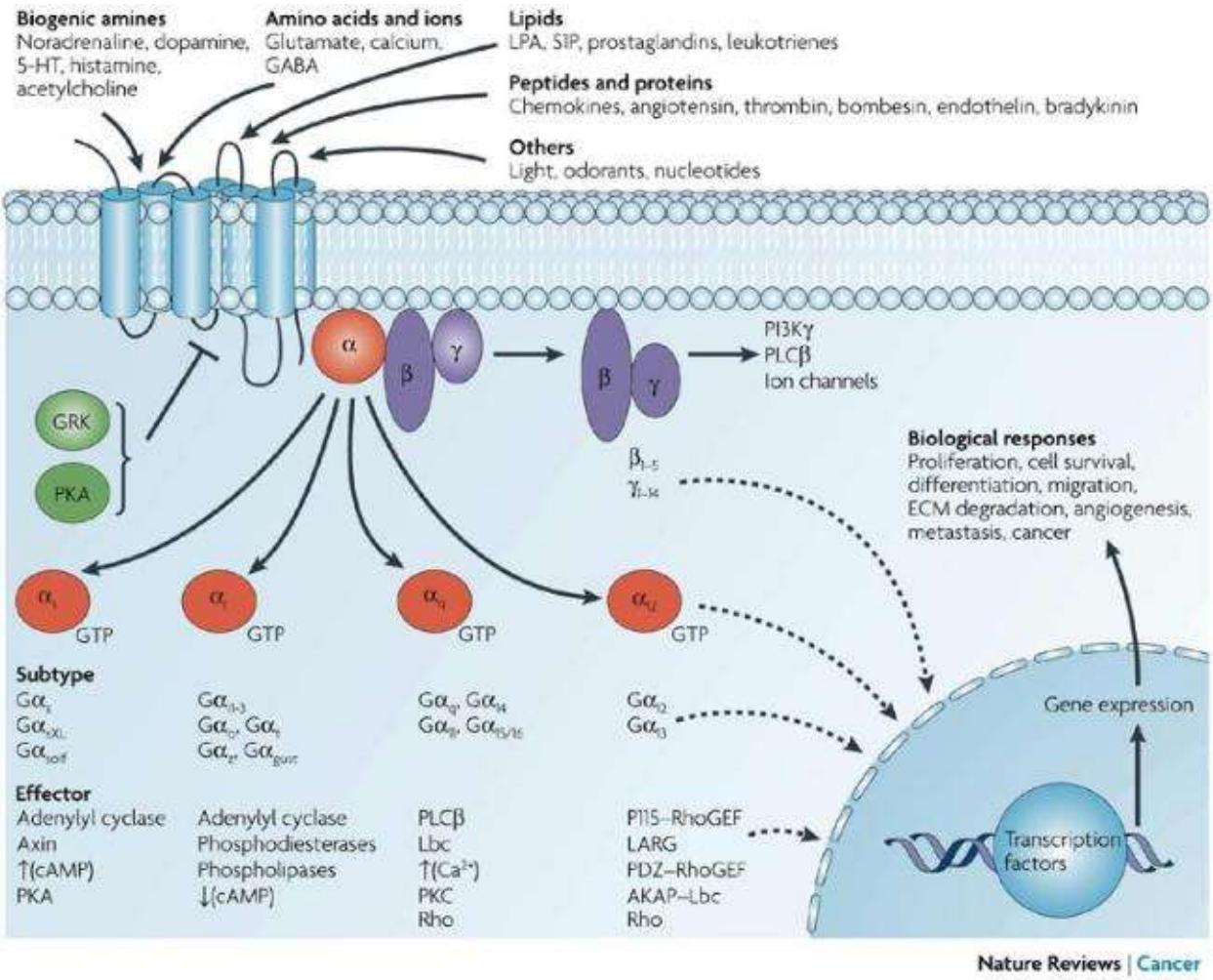


Fig 29

Figure 30 illustrates how the main pathways of G-protein signaling initiate.

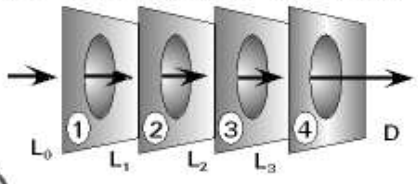


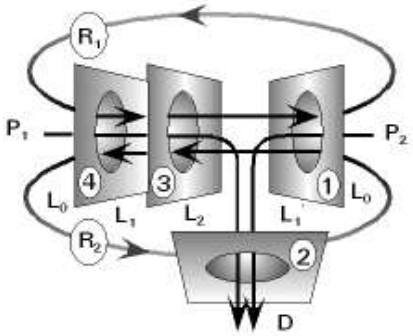
System 4 Terms:
Fig. 30

SYSTEM 4

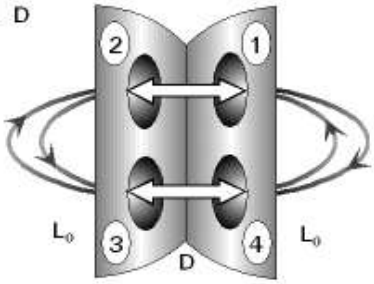
Terms 9, 3, & 6 are universal.
Terms 1, 2, 4, 5, 7 & 8 are particular and are shown in the expressive mode.

T9 - Discretionary Hierarchy



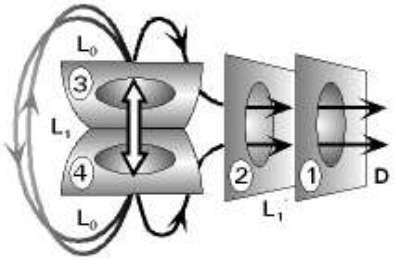


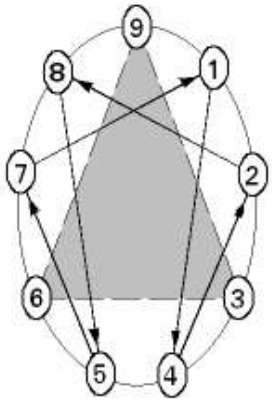
Response to Need - T8E



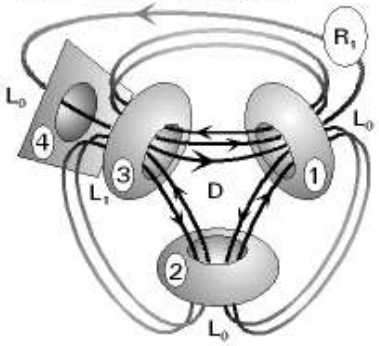
T1E - Perception of Need

Quantized Memory - T7E

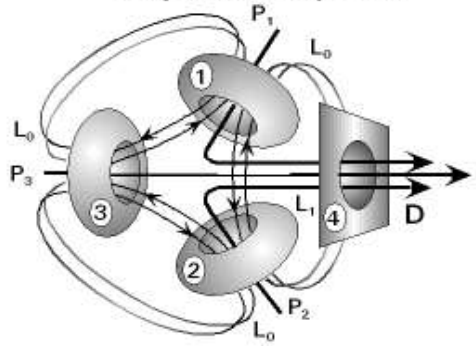




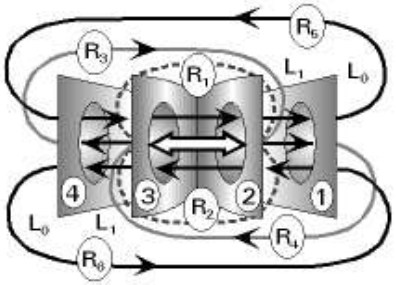
T2E - Idea Creation



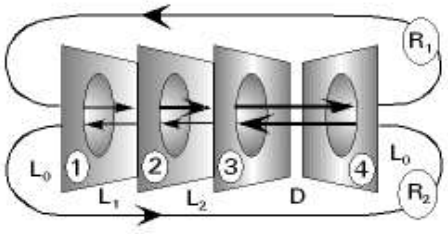
Corporeal Body - T6



T3 - Idea Transference



Physical Action - T5E



T4E - Organized Input

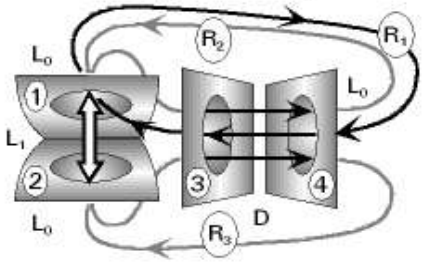


Fig. 31
System 4

System 4 Terms

Cell Overview

Primary Cilia, System & Mind