Gene Expression Organization

Robert Campbell 2011

Introduction:

This article deals with the sequential processes of gene transcription and translation. Copying RNA from DNA is called transcription. It precedes the translation from RNA into protein. Both processes are very complex and poorly understood although many of the factors involved are known and under study. New discoveries continually add to the mystery of how the cell works in intimate association with organs they constitute and the host human being. (DNA replication which precedes cell division will not be dealt with in this article.)

It will be shown how these two processes of transcription and translation generally correspond to the Term transformation Steps in the System 4 transform sequence. It should be recognized that this kind of complexity is hierarchically ordered in subsumed levels of increasing complexity consistent with the way the System elaborates within itself. In this respect the subsumed levels of complexity are distinguished from the more general levels that transcend and subsume them. This System 4 methodology thus has the advantage of simplifying the overall patterns of how Cells, Organs and Host work coherently together.

Within this overall pattern, the complexity within each Term transformation Step can then be assessed more readily. The implicit assumption that the whole human apparatus functions as an interconnected causal network of molecular processes operative on a non-hierarchical physical level erects formidable barriers to ever understanding how it all works together. There are overriding integrating principles implicit in the nature of the cosmic order itself. Random causal order is not consistent with the highly ordered universe that we find ourselves in. The System methodology embraces all possible varieties of phenomenal experience including a place for randomness.

The six particular Terms of System 4 transform through the six Term repeating sequence 1, 4, 2, 8, 5, 7. As in other cell articles the similarity of a cell to a large corporation will be useful in communicating the complexity of a cell in a meaningful way. Every business begins as an idea in the mind of one human being. As a one man business grows delegation proceeds into discrete interrelated areas of activity such as Marketing (T1- Assessing market needs and trends, distinct from Sales), Organization of Human Resources (T4- Personnel organized in departments), Product Development (T2- Engineering Product Design and Research), Sales (T8- Selling specific products and making specific sales projections), Production (5- Product manufacture or service), Finance (T7- Accounting, Budgeting and Financing operations). These six primary domains are common to all organizations. In a large corporation each of the six domains of the organization begins to distinguish six self-similar sub-domains within each domain as the complexity of the organization grows. The T1 Marketing domain is normally last to be delegated. (It does not create markets as in the sub-prime mortgage collapse. It identifies legitimate market needs and the capacity to respond.)

These six domains have their correlates in the organization of the human nervous system. A very general overview of how this works is given for the general reader in the website article Inside Our Three Brains. Two advanced articles show how it works synapse by synapse at Spinal and Cerebellum/Cerebral levels respectively. Following these two related articles in detail one can see how System 4 can be read down into subsumed levels inside the cell as it relates to Organs and Host. The spinal article is common to the vertebrate lineage from amphibians to humans. The Cerebellum article relates to human behavior. We simulate behavior in thought, language and feeling.

The complexity of Transcription and Translation will be reviewed in the context of how it conforms to the Term transformations of System 4. There will be some duplication of the other cell articles as they apply in this context.

Brief System 4 Review:

System 4 is generated by four active interfaces between a universal inside and a universal outside, neither of which can be known to the exclusion of the other. All we can know in experience is active interface processes between them. There are only nine possible ways that four active interfaces can relate to one another with respect to inside and outside and these nine ways define the nine Terms of System 4 which interact in a manner consistent with Systems 1, 2 and 3 that subsume and transcend System 4.

This hierarchical order is elaborated on in System 4 by a Primary and a Secondary Universal Set, each with a distinct but related transform sequence. Together the Universal Sets regulate three Particular Sets that transform through the repeating six Term sequence 1, 4, 2, 8, 5, 7 one transform Step apart. The Universal Sets complete their transform sequences in four Particular Steps such that three Cycles of transformation are needed to complete the expressive and regenerative sequences of each Particular Set. The regulatory role of orthogonal centrioles and their structural consistency with System 4 indicates that their microtubule arrangement channels System 4 patterned energy.

The four System 4 active interfaces constitute the Universal Hierarchy of the Primary Universal Set. In general parlance the hierarchy is prescribed as ***Idea*** gives direction to ***Knowledge***, which gives direction to ***Routine*** which gives direction to ***Form***. These four words have to be interpreted in context. For example the *Form* of human behavior is determined by *Idea*, *Knowledge* and *Routine* in that order.

Idea (1) → Knowledge (2) → Routine (3) →Form (4).

In a corporation the company ***Idea*** implicit in its product line directs the ***Knowledge*** implicitly invested in the company infrastructure that directs the ***Routines*** implicit in committing available resources to specific product cycles which directs the task cycles at the functional level of work that gives physical ***Form*** to end products. This defines four distinct levels of work. As they apply in this context they are called Managerial, Administrative, Supervisory and Functional work respectively.

Idea (integrating energy pattern) → ***Knowledge*** (vested in infrastructure cycles) → ***Routine*** (resource commitment to product cycles) → ***Form*** (task cycles of producing end products). For more detail see the website article Primary Cilia, the System & Mind.

The Particular Sets display Expressive and Regenerative modes to five of the six Terms for reasons described later, such that each Set goes through 7 Expressive and 5 Regenerative modes making 12 Steps in all, divided into 3 Cycles. In each Cycle insight into ***three polar dimensions*** regulates a balance between ***Performance***, ***Potential*** and ***Commitment*** that integrates space-time events since both modes of all Terms must be mutually reconciled.

There is meaning implicitly defined within each Term according to how the four Centers mutually interrelate as a whole. In the Regenerative mode of each Term the active interfaces 1 and 2 exchange places (also called Centers 1, 2, 3, 4).

There are two possible variants encountered in System 4, the normal one being the evolutionary variant. The other is called the involutionary variant and leads to disease, decay, death and fragmentation. The two variants are mutually exclusive because the expressive mode of one is the regenerative mode of the other. This allows the involutionary variant to feed on the evolutionary variant, while the evolutionary variant can redeem the energies of involutionary variants that may ultimately become extinct. In the involutionary variant Centers 3 and 4 exchange places. Values and meaning become inverted. Events evolve as ends in themselves such as the growth of cancers that feed on the Host rather than relating to the needs of the Host. Evolution has been a process of redeeming involutionary energies of species extinctions in stages.

The mechanics of gene expression will be reviewed with this general outline in mind. There will be more on System 4 later and more in separate articles. It takes patience to fully grasp.

Fig. 1

The Base Pair Codons of Genes:

DNA (deoxyribonucleic acid) consists of two helical stands of pentose sugar molecules called deoxyribose covalently joined together by phosphate groups (PO4). The two very longs strands are linked together by pairs of four nucleic bases. Thymine forms a weak hydrogen bond with Adenine and Cytosine forms a weak hydrogen bond with Guanine. When RNA (ribonucleic acid) transcribes a gene from the template strand of DNA the code is repeated but Thymine is replaced by Uracil and the pentose sugar molecules are ribose instead of deoxyribose with one less oxygen atom.

Groups of three base pairs constitute a codon. Each base pair is like a word that spells out a three word codon language. Twenty words are necessary to code for the twenty essential amino acids that combine in a specific order to make a protein. A linear series of codons specifies a specific gene with some codons indicating where the gene starts and stops. Some codons have side groups attached to indicate promoter, enhancer or repressor regions that influence gene transcription and its regulation. There are about 3 billion base pairs in the human genome and over twenty thousand genes.

Genes code for various kinds of RNA. Messenger RNA designated mRNA codes for a potentially unlimited number of specific proteins of various lengths from small peptides less than 40 amino acids in length to huge proteins thousands of amino acid sequences in length. Transfer RNA designated tRNA comes in 20 varieties, each one tailor made with an anti-codon to identify and collect each specific amino acid and bring it to ribosomes for assembly in the specific codon order designated by mRNA. Ribosomal RNA (rRNA) comes in four varieties that combine with special proteins to form ribosomes that have a common structure in animal species. Non-coding RNAs (ncRNA) such as small nuclear RNA (snRNA), small nucleolar RNA (snoRNA), small interfering RNA (siRNA), micro RNA (miRNAs number over 1000 varieties) and long ncRNA (lncRNAs number in the tens of thousands) influence the transcription and regulation of genes including DNA sequences that code for them.

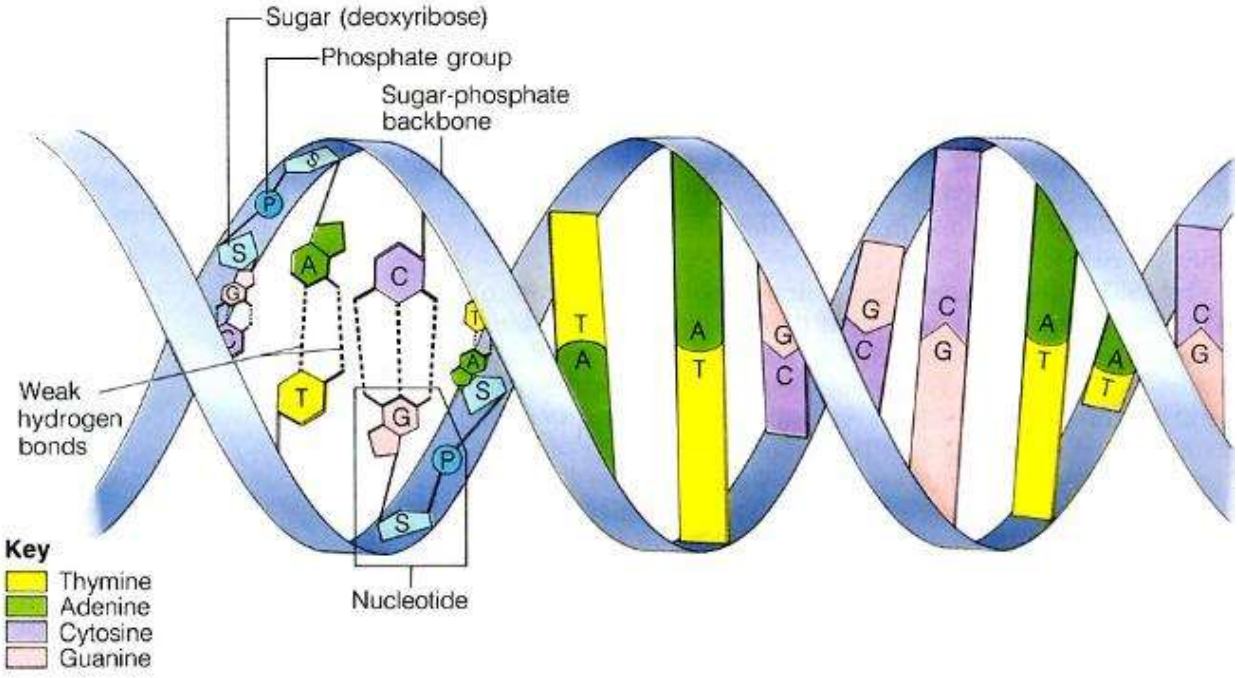


Fig. 2

A nucleotide is the monomer structural unit of nucleotide chains that form the nucleic acids DNA and RNA. Other nucleotides such as ATP, ADP, AMP, GTP, GMP and cAMP are involved in intracellular process such as signaling and energy production. The nucleotide consists of a heterocyclic nucleobase (T, A, C & G) , a pentose sugar (S) like ribose or deoxyribose, and a phosphate or polyphosphate group (P). The members of the pentose sugar ring are numbered from 1' to 5' so the phosphate groups that link the sugar molecules are attached to either the 5' end or the 3' end. Transcription of RNA proceeds by adding nucleotides to its 3' end, that is, in the 5' to 3' direction. Either strand of DNA may serve as the template which is read in the 3' to 5' direction.

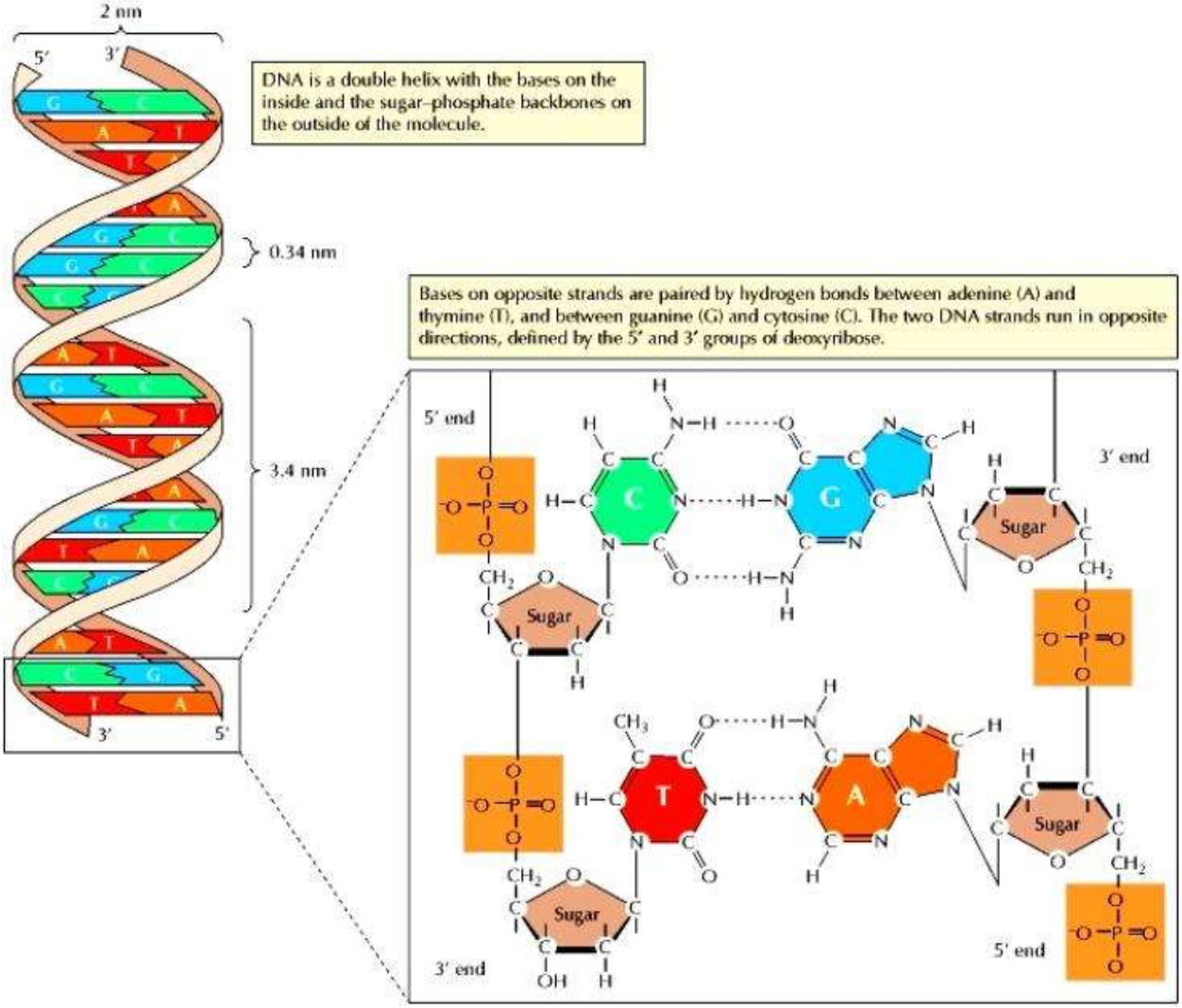


Fig. 3

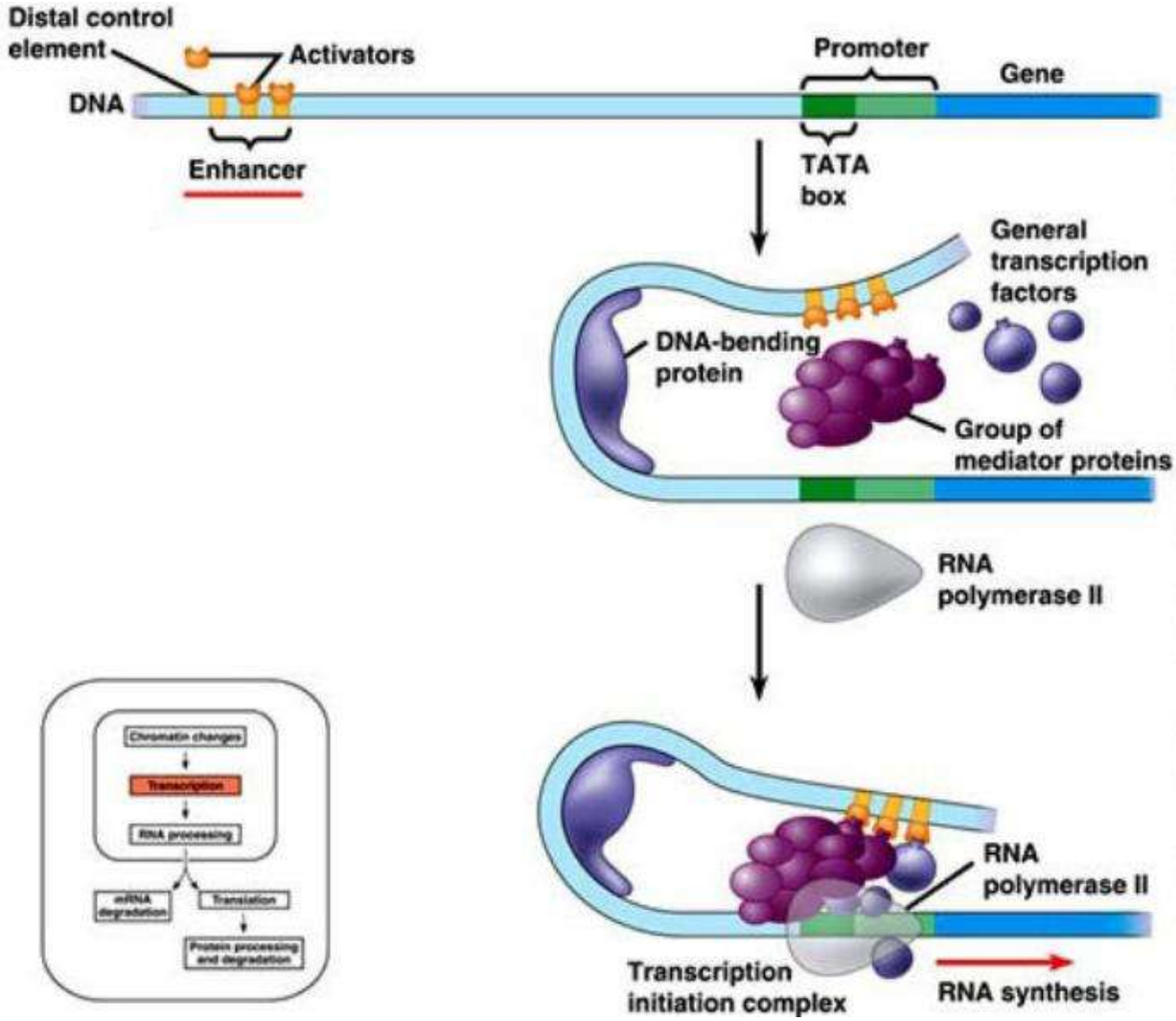
Transcription Factors and Co-factors:

In eukaryotic cells Polymerase I (Pol I) transcribes rRNAs except for the 5S rRNA, which is synthesized by RNA Polymerase III (Pol III). Over 50% of all RNA transcribed in a eukaryotic cell is ribosomal rRNA that is transcribed in the nucleolus where several hundred copies of rRNA genes are present, arranged as tandem head-to-tail repeats. Pol I transcribes one large transcript, encoding an rDNA gene over and over again. This gene encodes the 18S, the 5.8S, and the 28S RNA molecules of the ribosome. Each large transcript is cleaved by snoRNA`s to produce three of the rRNA molecules. The fourth 5S ribosomal RNA is transcribed by Polymerase III.

Because of the simplicity of Pol I transcription, it is the fastest-acting polymerase. Because the three Pol I rRNAs that are transcribed together in equal amounts need 5S rRNA that is transcribed by Pol III to form ribosome sub units, and because Pol III activity is linked to Pol II activity by other ncRNAs, the number of Ribosome subunits transcribed is adjusted to Pol II mRNA transcription for proteins. An appropriate number of ribosomes for translation to protein can thus be synthesized according to needs dictated by mRNA transcription. System 4 regenerative modes anticipate needs that regulate expressive modes, so Pol III has a regenerative role in this case.

Pol II is a large complex enzyme that clamps around the template strand of DNA and moves along it catalyzing the transcription of gene sequences to synthesize precursors of mRNA and most snRNAs and microRNAs. It consists of a complex of 12 subunits that interact and have a total atomic mass of 550 kDA (roughly equivalent 550,000 hydrogen atoms). The subunits themselves are encoded as genes that must be transcribed and that interact in groups to form Pol II. Enzymes can catalyze up to several million reactions per second depending on conditions. Otherwise the process would be hopelessly slow. Pol II works in conjunction with a large and highly complex variety of protein transcription factors and co-factors.

RNA polymerase III (Pol III) transcribes DNA to synthesize ribosomal 5S rRNA, transfer tRNA and other small RNAs. The genes transcribed by RNA Pol III fall in the category of regenerative "housekeeping" genes required in all cell types and in most environmental conditions. Therefore the regulation of Pol III transcription is primarily tied to the regulation of cell growth and the cell cycle, and it requires fewer regulatory proteins than RNA Pol II.


Distal control element
Activators
DNA
Enhancer
Promoter
Gene
TATA box
General transcription factors
DNA-bending protein
Group of mediator proteins
RNA polymerase II
RNA polymerase II
Transcription initiation complex
RNA synthesis
Chromatin changes
Transcription
RNA processing
mRNA degradation
Translation
Protein processing and degradation

An enhancer is a short region of DNA that can bind proteins like transcription factors to enhance transcription of genes.

Most are redundant copies of noncoding DNA sequences. Are they because of poor genomic housekeeping, or do they function to improve the organism's chances of survival?

David Stern at Princeton University attacked this question by looking at duplicate or "shadow" versions of enhancers. When he knocked out duplicate enhancers for the fruit fly gene ***shavenbaby***, which codes for larval hair growth, he found that the flies were unable to produce hairs in non-optimal environments, supporting the hypothesis that redundant genetic elements make an organism more robust genetically.

Read more: Shivering Shavenbaby - in The Scientist
Vol 24 - Issue 10 - pg 66 - October 1, 2010

A Note on Ribosomes:

The two ribosome subunits that combine in the cytoplasm to translate mRNA into protein also consist of a complex of about 80 proteins. These proteins are likewise translated from mRNA in the cytoplasm and imported back into the nucleus for ribosome sub-unit assembly before the sub-units can be exported back to the cytosol to translate mRNA into protein. The pre-rRNAs are subject to covalent nucleotide modifications before they assemble with the 80 ribosomal proteins and the independently transcribed 5S rRNA.

Fig. 4

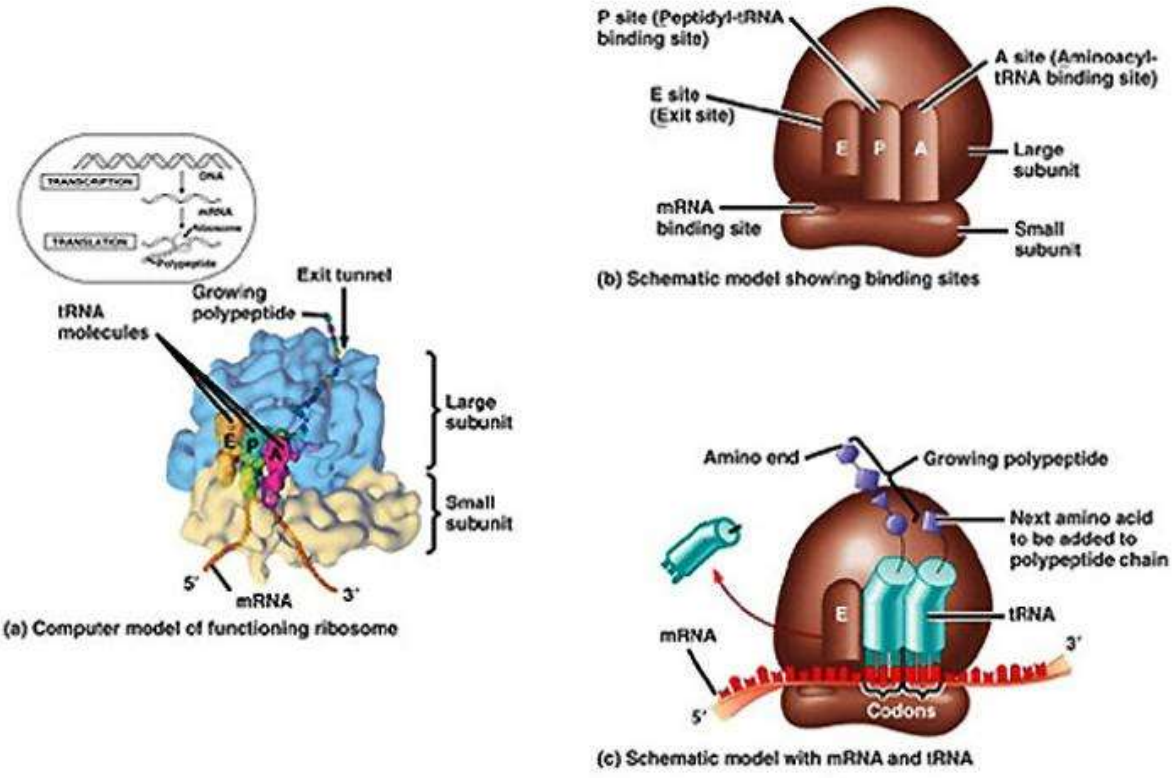


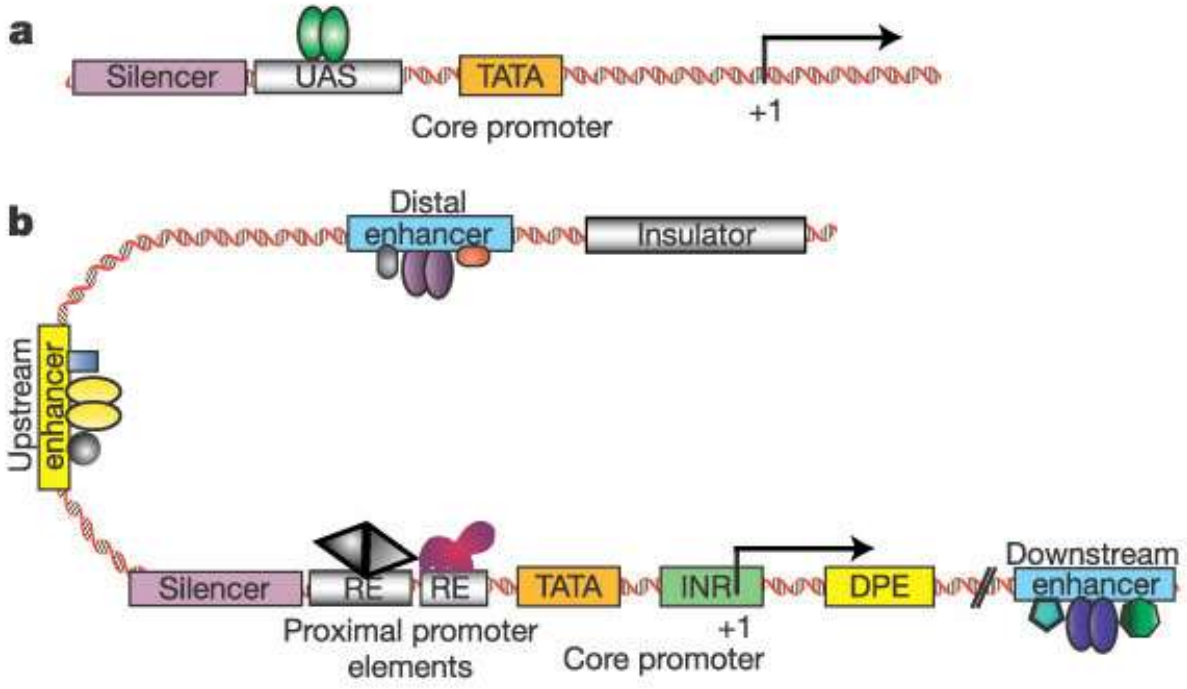
Fig. 5

Given the demand for equal-molar amounts of rRNA and ribosomal proteins during ribosome synthesis, the transcription of rRNAs and the mRNAs for ribosomal proteins must be coordinated. A complex network of transcription factors collectively regulates the expression of rRNA, ribosomal protein genes and ribosome biosynthesis factors (so-called ribi factors). These regenerative Cell processes must be coordinated with the distributed needs of specific Organs of the Host according to available energy resources. Since ribosome synthesis entails very high energy consumption, this emphasizes the basic balancing role for primary cilia and centrioles that channel System 4.

Transcription Complexity with Complex Creatures:

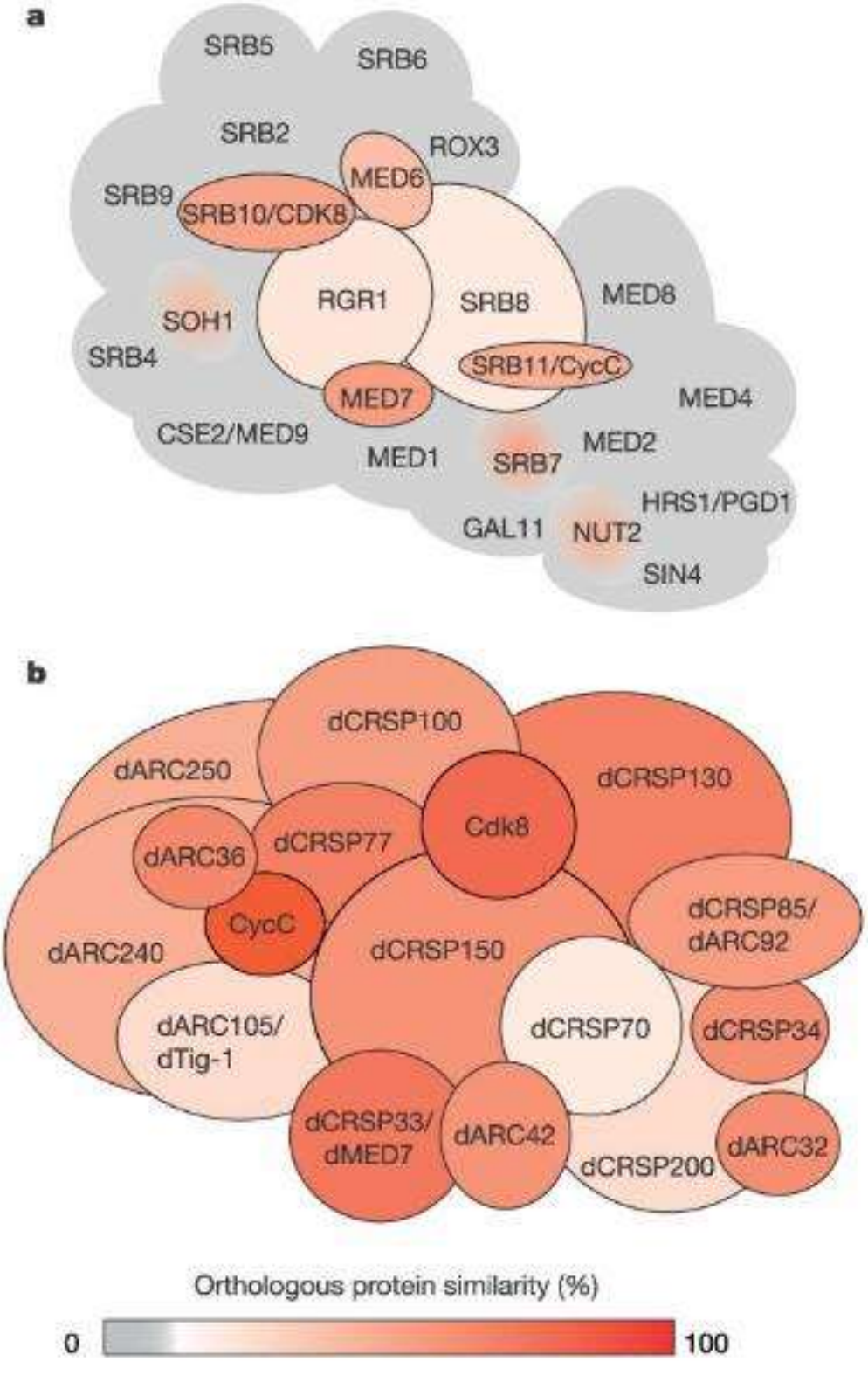
The complexity of transcription initiation has increased dramatically from single celled creatures such as yeast to multi-celled creatures from flies to humans. This is illustrated in the following three illustrations from the article *Transcription Regulation & Animal Diversity,* Michael Levine and Robert Tjian, ***Nature 424*, 147-151(10 July 2003)**.

Simple One Cell vs. Multi-cell (Metazoan) Animal Transcription Initiation Complexes



a, Simple eukaryotic transcriptional unit as in yeast. A simple core promoter (TATA meaning Thymine-Adenine base pair repeats), upstream activator sequence (UAS) and silencer element spaced within 100–200 bp of the TATA box that is typically found in unicellular eukaryotes such as yeast.
b, Complex metazoan (animal) transcriptional control modules. A complex arrangement of multiple clustered enhancer modules interspersed with silencer and insulator elements which can be located 10–50 kb (kilobases) either upstream or downstream of a composite core promoter containing TATA box (TATA), Initiator sequences (INR), and downstream promoter elements (DPE).

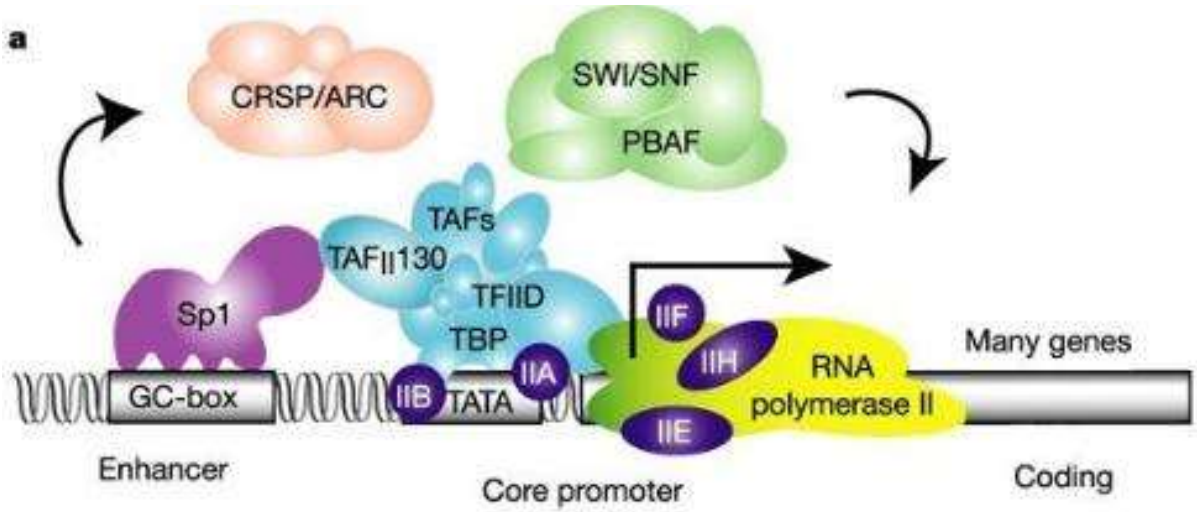
Fig. 6

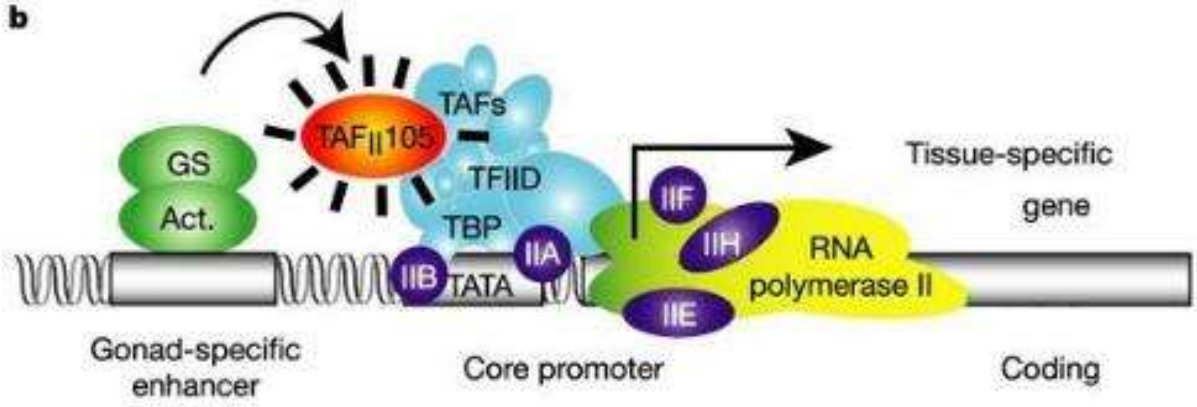

a
SRB5
SRB6
SRB2
ROX3
MED6
SRB9
SRB10/CDK8
RGR1
SRB8
MED8
SOH1
SRB4
SRB11/CycC
MED7
MED4
CSE2/MED9
MED1
SRB7
MED2
HRS1/PGD1
GAL11
NUT2
SIN4
b
dCRSP100
dARC250
dCRSP130
Cdk8
dARC36
dCRSP77
CycC
dCRSP85/
dARC92
dARC240
dCRSP150
dARC105/
dTig-1
dCRSP70
dCRSP34
dCRSP33/
dMED7
dARC42
dCRSP200
dARC32
Orthologous protein similarity (%)
0
100

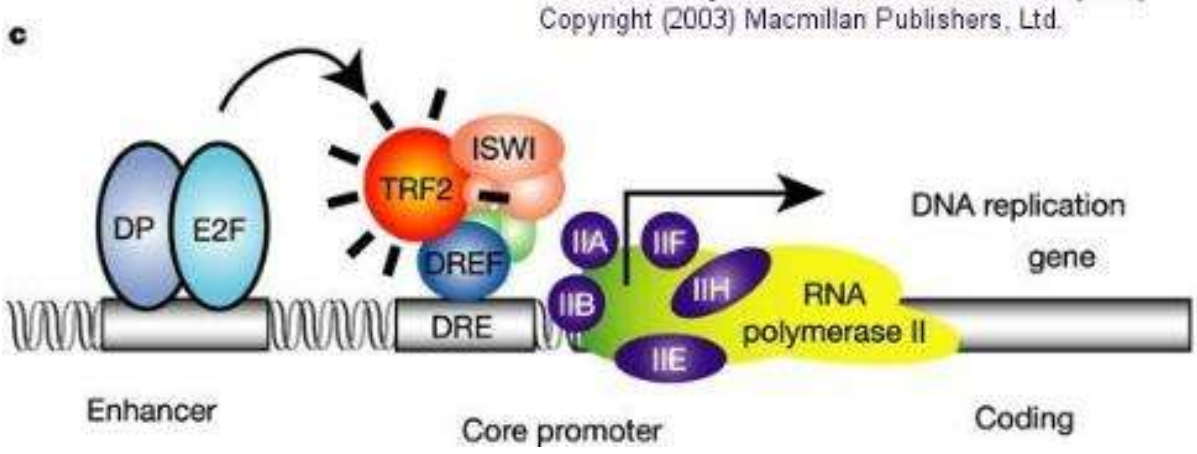
Critical components of large multi-subunit cofactor complexes such as mediator and CRSP/ARC have diversified both structurally and functionally, particularly when comparing uni-cellular eukaryotes to their milticellular metazoan animal counterparts.

a, Yeast mediator versus human cofactor complex. Most of the yeast mediator subunits display very limited, if any, sequence similarity to subunits of human CRSP/ARC although these two cofactor complexes are thought to function in an analogous manner to potentiate RNA Pol II transcription.
b, Drosophila (fruit fly) versus human cofactor complex. Even some of the CRSP/ARC subunits have significantly diverged between Drosophila and human, although many share conserved regions. We have colour-coded the extent of amino acid sequence similarity between different orthologous co-activator subunits from yeast, Drosophila and human. Grey is used to depict yeast subunits with no counterparts in Drosophila or humans. White or lightly shaded components represent very little structural conservation (17–20%) while darkly shaded orange and red represent highly conserved (40–80%) subunits.

Fig. 8







Diversified metazoan transcription initiation complexes:

- **a,** The transcriptional apparatus can be subdivided into three broad classes of multi-subunit ensembles that include the RNA polymerase II core complex and associated general transcription factors (TFIIA, -B,-D,-E,-F and -H), multi-subunit cofactors (mediator, CRSP, TRAP, ARC/DRIP, and so on) and various chromatin modifying complexes (SWI/SNF, PBAF, ACF, NURF and RSF).
- **b, c,** Metazoan organisms have evolved multiple gene-selective and tissue-specific TFIID-like assemblies by using alternative TAFs (TBP-associated factors such as the ovarian-specific TAF105) as well as TRFs (TBP-related factors such as TRF2 in Drosophila (fruit flies) and mice to mediate the formation of specialized RNA polymerase initiation complexes that direct the transcription of tissue-specific and gene-selective programmes of expression.

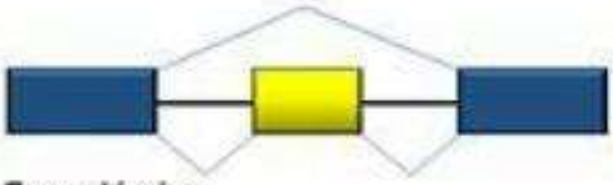
Fig. 7

Exons, Introns and Alternative Splicing:

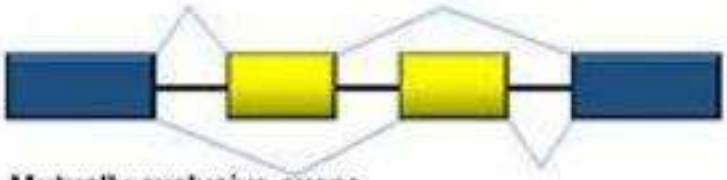
Only about 1.5% of human DNA consists of exon segments in genes that code for proteins. The remainder includes introns that are spaced between exons in gene sequences, including within gene sequences that code for tRNA and rRNA, plus other non-coding base pair sequences in the genome. Introns are 8.4 times more numerous than exons on average and often have much longer sequences. There are many more proteins than the estimated 21,000 to 25,000 protein coding genes in the human genome. The difference is due to alternative splicing of transcribed pre RNA and/or various modifications of protein after it is translated from RNA. In humans about 95% of genes are alternatively spliced to code for a huge variety of proteins. In this respect introns and non-coding sequences represent regenerative modes that regulate the expressive modes of genes.

In alternative splicing the exons of the pre-mRNA transcribed are reconnected in multiple ways. The resulting different mRNA's may be translated into different protein isoforms. Thus, a single gene may code for multiple proteins.

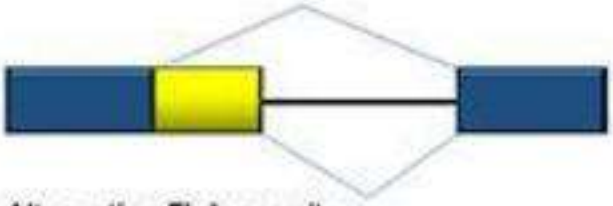
At least five basic modes of alternative splicing are generally recognized:



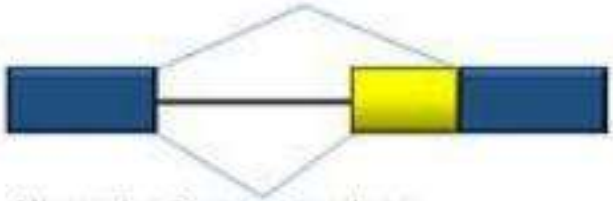
Exon skipping



Mutually exclusive exons



Alternative 5' donor sites



Alternative 3' acceptor sites

Intron retention

- Exon skipping or cassette exon: in this case, an exon may be spliced out of the primary transcript or retained. This is the most common mode in mammalian pre-mRNAs.

- Mutually exclusive exons: One of two exons is retained in mRNAs after splicing, but not both.

- Alternative donor site: An alternative 5' splice junction (donor site) is used, changing the 3' boundary of the upstream exon.

- Alternative acceptor site: An alternative 3' splice junction (acceptor site) is used, changing the 5' boundary of the downstream exon.

- Intron retention: A sequence may be spliced out as an intron or simply retained. This is distinguished from exon skipping because the retained sequence is not flanked by introns. If the retained intron is in the coding region, the intron must encode amino acids in frame with the neighboring exons, or with a stop codon or else a shift in the reading frame will cause the protein to be non-functional. This is the rarest mode in mammals.

Fig. 9

Transposons:

Transposons are DNA sequences that can move or transpose themselves to new positions within the genome of a single cell. The mechanism can be either "copy and paste" or "cut and paste". Transposition can create phenotype mutations and alter the cell's genome size.

Class I (Retrotransposons): They copy themselves in two stages, first from DNA to RNA by transcription, then from RNA back to DNA by reverse transcription. The DNA copy is then inserted into the genome in a new position. Reverse transcription is catalyzed by a reverse transcriptase, which is often coded by the transposon itself. Retrotransposons behave very similarly to retroviruses, such as HIV. They represent an involutionary variant of System 4 associated with disease and decay.

Class II (DNA transposons): The class two cut-and-paste transposition mechanisms do not involve an RNA intermediate. These transpositions are catalyzed by various types of transposase enzymes. This results in target site duplication and the insertion sites of DNA transposons may be identified by short direct repeats (a staggered cut in the target DNA filled by DNA polymerase) followed by inverted repeats (which are important for the transposon excision by transposase). The duplications at the target site can result in gene duplication, which plays an important role in evolution. They generally represent an evolutionary variant of System 4.

Both classes of transposons may lose their ability to synthesise the needed reverse transcriptase or transposase enzymes through mutation, yet continue to jump through the genome because other transposons are still producing the necessary enzymes. Hence, DNA transposons can be classified as either "autonomous" or "non-autonomous". Autonomous transposons have an intact gene that encodes an active transposase enzyme; the transposon does not need another source of transposase for its transposition. In contrast, non-autonomous transposons encode defective polypeptides and accordingly require transposase from another source.

Retroviruses can be considered transposable elements. After entering a host cell and converting their RNA into DNA, retroviruses integrate this DNA into the DNA of the host cell. The integrated DNA form (provirus) of the retrovirus is viewed as a particularly specialized form of eukaryotic retrotransposon, which is able to encode RNA intermediates that usually can leave the host cells and infect other cells. This is an involutionary variant of System 4 that feeds on the evolutionary variant.

Genotype versus Phenotype:

The **genotype** is the genetic makeup of the cells in an individual (i.e. the specific allele makeup of the individual) usually with reference to a specific characteristic under consideration. For instance, the human CFTR gene, which encodes a protein that transports chloride ions across cell membranes, can be dominant (A) as the normal version of the gene, or recessive (a) as a mutated version of the gene. Individuals receiving two recessive alleles from their parents (aa rather than Aa or AA) will be diagnosed with cystic fibrosis. One allele of the gene comes from each parent. One of each parent's two alleles can be recessive (a). This case is another involutionary example of System 4.

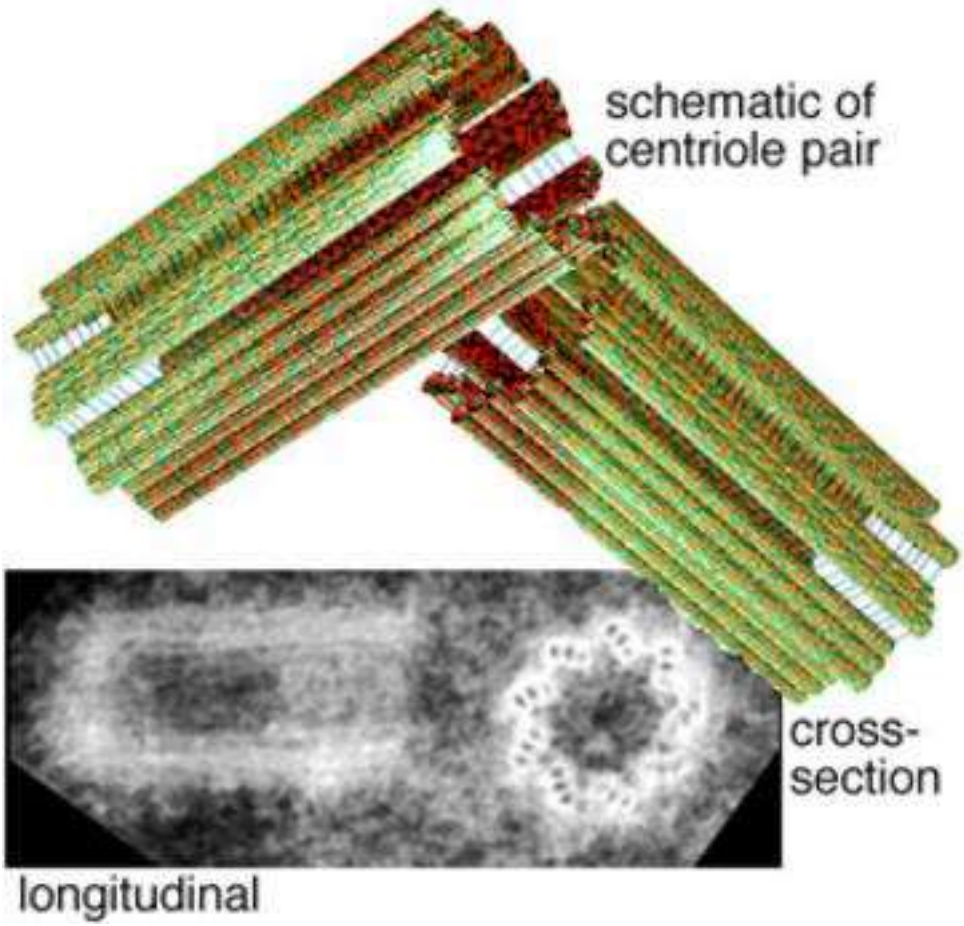
The **phenotype** is the "outward, physical manifestation" of the individual. These are the physical parts, the sum of the atoms, molecules, macromolecules, cells, structures, metabolism, energy utilization, tissues, organs, reflexes and behaviors; anything that is part of their observable structure, function or behavior in relation to the environment. It is generally accepted that inherited genotype, transmitted epigenetic factors, and non-hereditary environmental variation contribute to the phenotype of an individual.

There are a variety of definitions for the phenotype, Some would include a beaver dam in the phenotype of a beaver or a bird's nest in the phenotype of a bird. The phenotype does not include value judgments associated with behavior such as where to build the dam or how high, how much land to flood if it is a collective effort, where to build a house in the pond and so on. This requires a value assessment of the specific situation. Beavers are clever. Likewise the design of the bird's nest tends to be characteristic of each species but birds must choose specific mates, decide where to build their nest to be safe from predators, where to collect twigs and other nest materials, where best to hunt food for nestlings and so on. These are value judgments distinct from genotype and phenotype.

The Human Host and Primary Cilia:

A human individual may be invested with a broad range of talents rather like the capabilities of a variety of species. A human being can have a much greater diversity of possible attributes and capabilities than other species. Some people may have a propensity to be artistic, musical, clever, intuitive, deceitful, honest, corrupt, cooperative, stubborn, good at sports, and so on. A natural talent, or alternatively a natural handicap, does not determine how the talent or handicap will be exercised, however. Natural talents can be wasted or further developed just as handicaps can often be compensated for creatively, and just as character flaws can either be redeemed or fostered. This concerns value judgements that derive from how we seek to balance the three polar insights.

Fig 10b



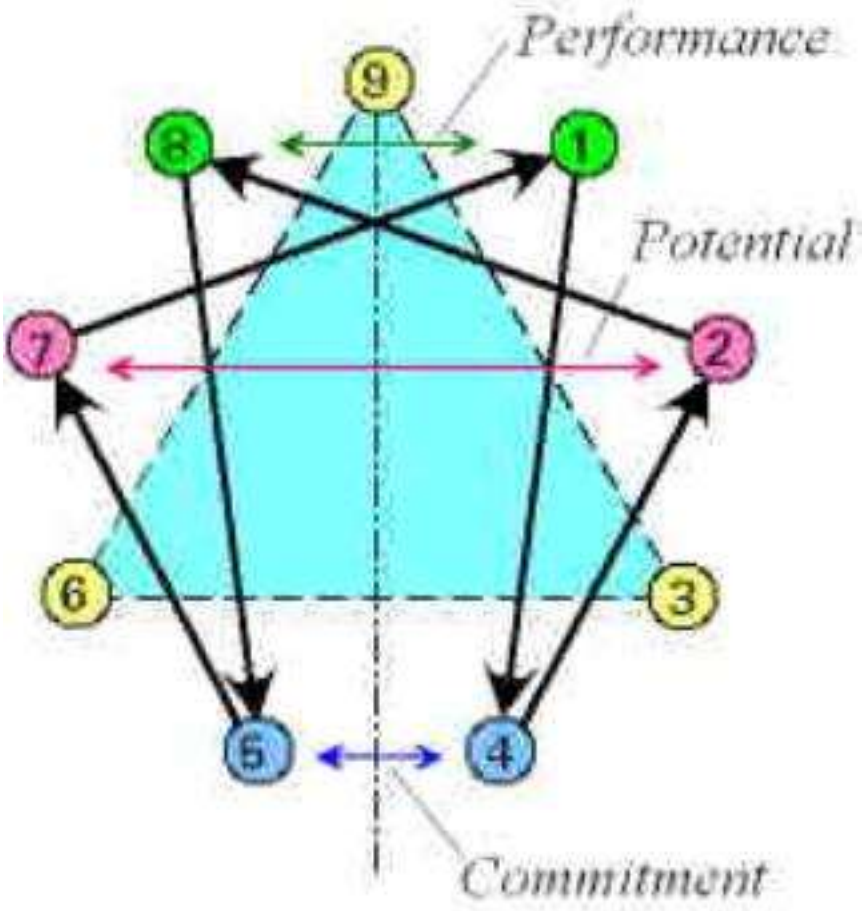


Fig. 10a

The phenotype does not causally pre-determine how we make value judgments. Language empowers us to plan ahead, anticipate a future result and make intelligent choices accordingly that can direct complex behavior over long periods of time. The way the human Host does this influences the balance with Organs and Cells. At the cellular level this intimate relationship is mediated by primary cilia and orthogonal centriole pairs consistent with the way that System 4 works. An orthogonal centriole pair each with 9 triplet microtubules is illustrated in Figure 10a.

In any business organization there are only six primary domains that are self-similar to those of a human individual consistent with System 4. The six Particular Terms of System 4 work in polar pairs to provide creative insight into the right-brain **Potential** Dimension (Product or Idea Development T2 is funded by Resource Capacity T7), the left-brain **Commitment** Dimension (Product execution or behavior T5 requires an Organizational context T4), and the emotional limbic brain **Performance** Dimension (Sales T8 can only be assessed relative to Market Perception T1). The three polar dimensions of Figure 10b are mutually interdependent and seek a creative balance. They are always present.

In business organizations these six domains are delegated in a vast variety of ways depending on the nature of the business, whether manufacturing airplanes, TV sets, or cars, or making an array of small articles, or providing services of many kinds, or whether a business is local or global and so on. The infrastructure of the business may be considered its phenotype but how wisely that infrastructure is assembled and used depends on human value judgments that are not determined by phenotype. Value judgments are determined by how human insight into the three Polar Dimensions is sustained in an ongoing creative balance. Some businesses succeed while others with equal access to resources flounder or fail, just as some humans fare better than others.

A creative balance is demanded by the three Cycles of nine Term transformations of System 4. It is facilitated at the cellular level by how the two orthogonal centrioles channel the patterned energy dynamics of System 4 as it relates internally to the Cell and externally to Organs and Host. The mother centriole forms the basal body of the primary cilium that extends from each cell like an antenna in communication with Organs and Host consistent with System 5 as outlined in the article of Primary Cilia the System and Mind. Cells and Organs constrain the Host and also respond to the needs of the Host.

Gene Imprinting:

Each gene is represented by two copies, or alleles, with one copy inherited from each parent at fertilization. Imprinted alleles are silenced such that the affected genes are either expressed only from the non-imprinted allele inherited from the mother, or from the non-imprinted allele inherited from the father. Genomic imprinting is an epigenetic process that involves methylation and histone modifications without altering the genetic sequence. These epigenetic marks are established in the germline during gametogenesis and maintained throughout all somatic cells of an organism. Appropriate expression of imprinted genes is important for normal development. Around 80% of imprinted genes are found in clusters called imprinted domains, suggesting a level of coordinated control. For the vast majority of autosomal genes (not in sex chromosomes), expression occurs from both alleles. In mammals, however, a small proportion (<1%) of genes are imprinted, meaning that gene expression occurs from only one allele inherited from either the mother or the father.

Reprogramming of methylation patterns in gametes is essential to sex-specific inheritance of imprinted genes and assures exclusive harboring of female and male specific imprinted patterns in maternal and paternal gametes, respectively. The loss of genomic imprinting can lead to a variety of disorders. The establishment of imprints is a poorly understood procedure that reprograms the entire genome. This is important because accurate imprints must be passed on to the next generation. In other words, in males, all cells contain one set of chromosomes with male imprints (from the father) and another set with female imprints (from the mother), but when these chromosomes are passed on to the next generation, both sets in the germ cells must be reprogrammed to contain male imprints which account for the paternal contribution. Likewise, in females reprogramming is needed so that female-specific imprints are passed on to the next generation with maternal methylation patterns. The primary difference between methylated genes and imprinted genes is that the latter remain inactive in all cells whereas normal methylated genes can be activated and deactivated by signals in differentiated cells. Imprinting can have either evolutionary or involutionary influences.

Epigenetic Factors Can Result in Unlimited Phenotype Varieties:

Epigenetics refers to overriding heritable changes (over rounds of cell division and sometimes over generations) that do not involve changes to the underlying DNA. Epigenetic traits exist on top of or in addition to the traditional molecular basis for inheritance. They help determine the phenotype of individuals and can display either evolutionay or involutionary variants of System 4 each with expressive and regenerative modes such that involutionary variants may be redeemed.

Epigenetics involves DNA and chromatin modifications that play a critical role in regulating the expression of genes without altering their sequence of DNA codons. Although the genotype of most cells of any individual is the same (with the exception of gametes and cells of the immune system), cellular phenotypes can differ radically. This is influenced by epigenetic regulation particularly during cell differentiation and embryo morphogenesis. There are more than 50 trillion cells in the human body and several hundred different human cell types.

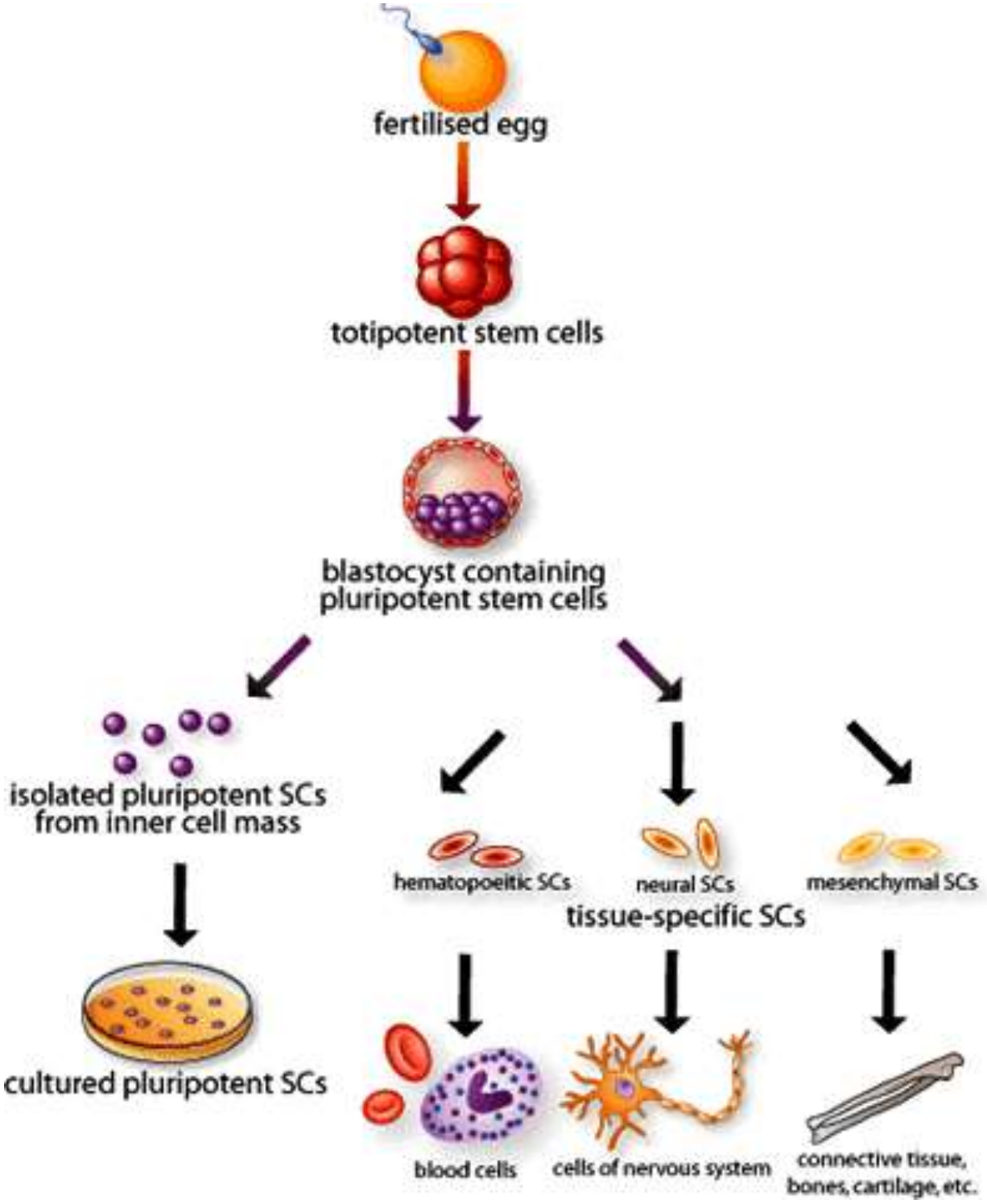

fertilised egg
totipotent stem cells
blastocyst containing
pluripotent stem cells
isolated pluripotent SCs
from inner cell mass
cultured pluripotent SCs
hematopoeitic SCs
neural SCs
mesenchymal SCs
tissue-specific SCs
blood cells
cells of nervous system
connective tissue,
bones, cartilage, etc.

Fig. 11

Once the cell phenotype is established, genomes of somatic cells become tissue-specific patterns of gene expression, generation after generation. This heritability of epigenetic information has been called an 'epigenetic inheritance system'. Even after the epigenetic profiles are established, a substantial degree of epigenetic variation can be generated during the mitotic divisions of a cell in the absence of specific environmental factors which may also result in epigenetic modifications.

Epigenetic factors are illustrated in Figure 12. Methylation adds methyl groups (CH3) to DNA Cytosine-phosphate-Guanine (CpG) nucleotide sequences distributed with respect to specific gene sequences. This may affect gene transcription through various mechanisms. The methylation pattern is heritable after cell division and it is important in cell differentiation during development.

A large variety of epigenetic factors can attach to histone "tails" in addition to protein interactions that can occur between the eight histone protein monomers that constitute the spool of each nucleosome. The significance of all these modifications is not well understood, but they do influence transcription, DNA repair, DNA replication and chromatin condensation. A "histone code" theory is being tested to determine if combinations of histone modifications can be used to predict changes in gene expression. For example, lysine acetylation is associated with transcriptionally active DNA, while the effects (i.e. activation or repression of transcription) of lysine and arginine methylation vary by location of these amino acids, number of methyl groups and proximity to a gene promoter. In any case the mutually exclusive evolutionary and involutionary variants of System 4 play a role.

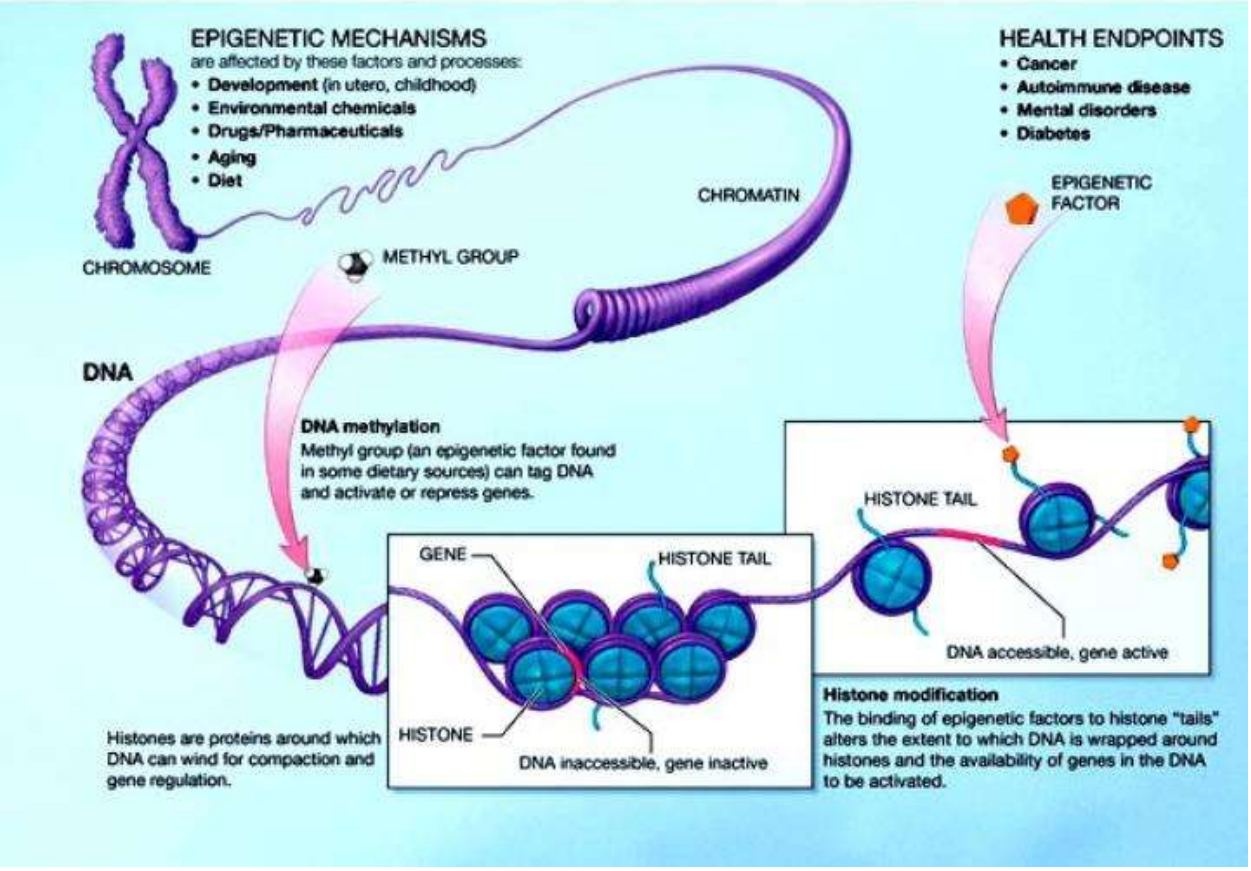


Fig. 12

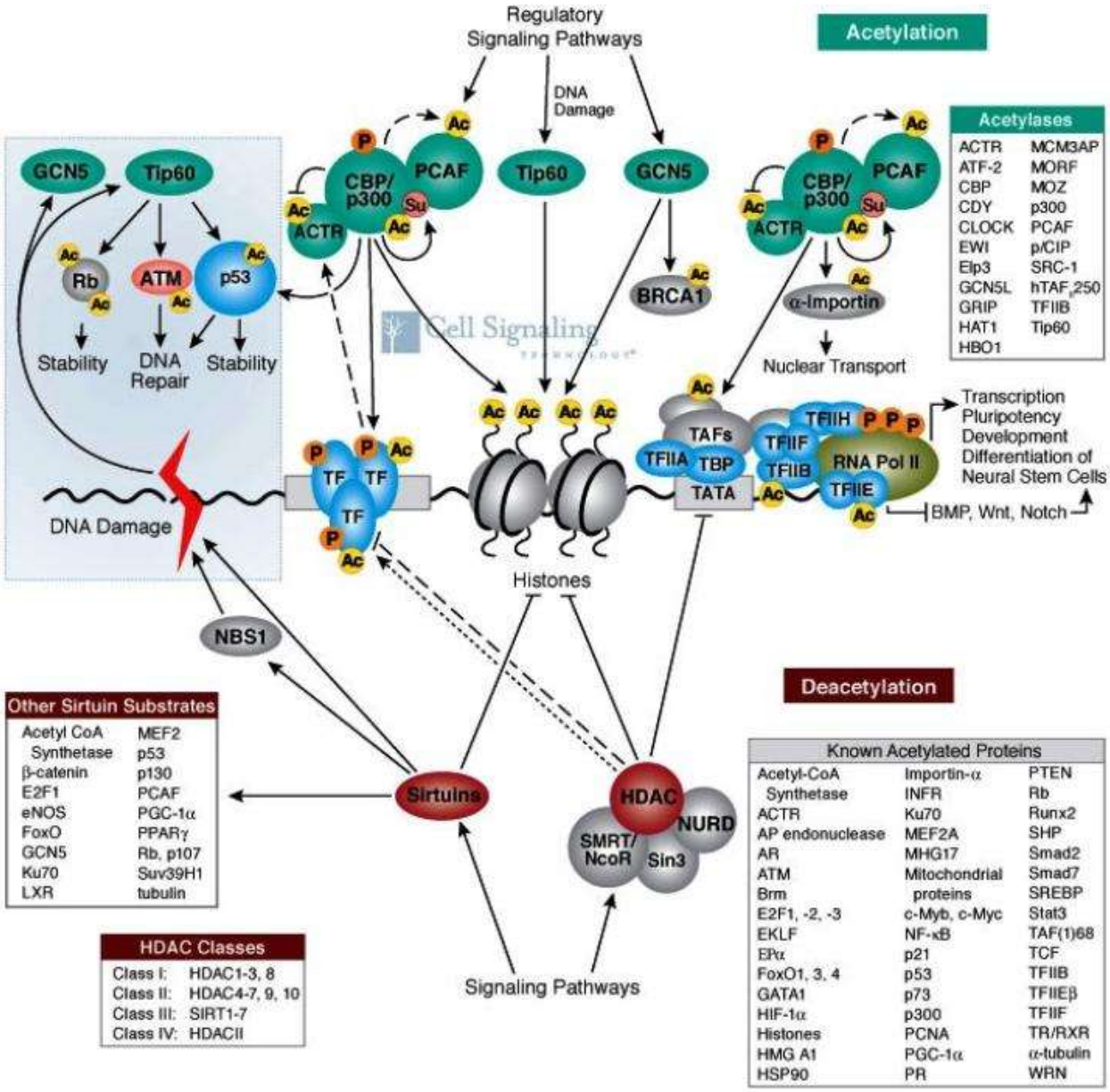
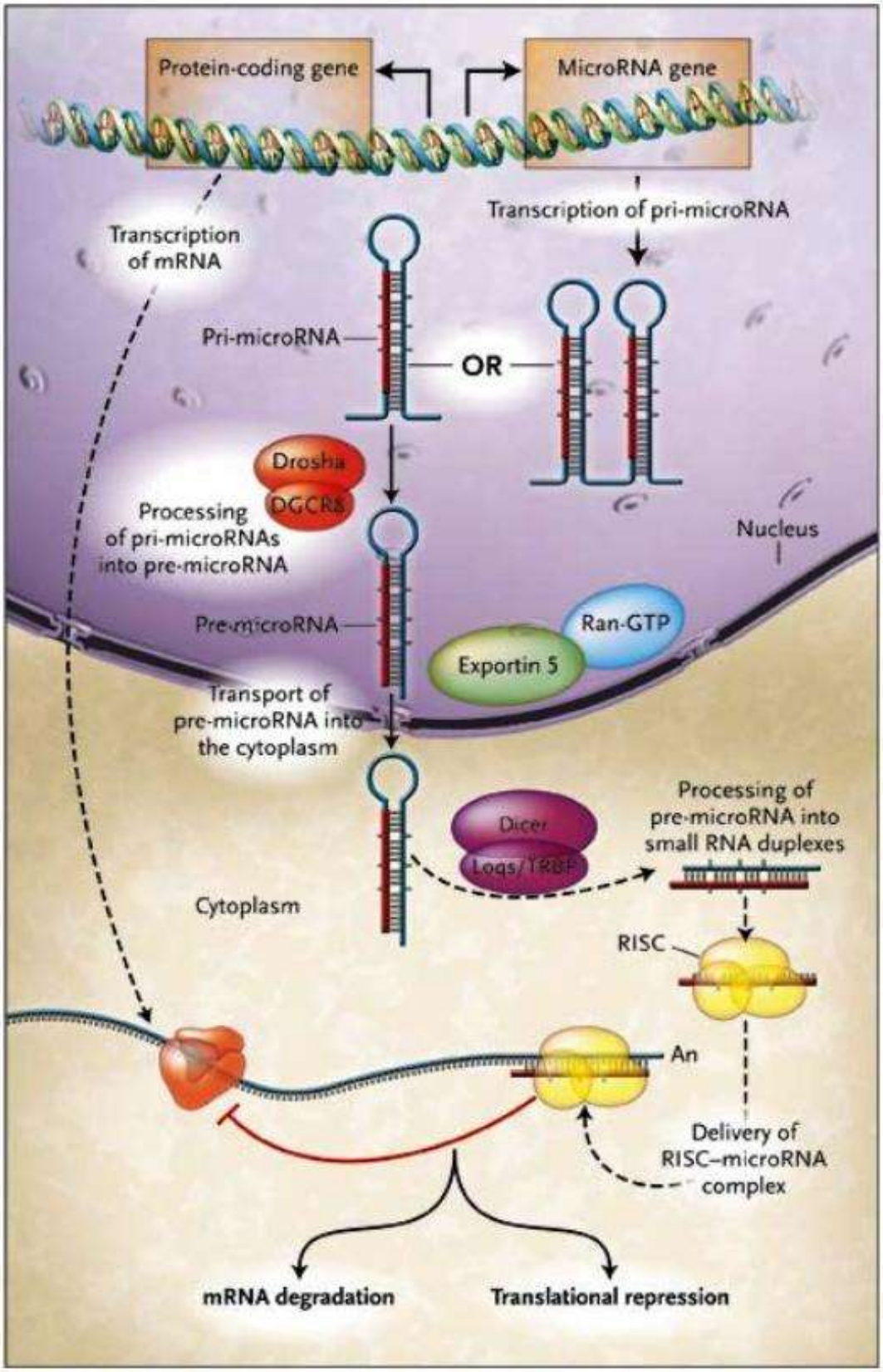

Regulatory Signaling Pathways
DNA Damage
Acetylation
Acetylases
ACTR MCM3AP
ATF-2 MORF
CBP MOZ
CDY p300
CLOCK PCAF
EWI p/CIP
Elp3 SRC-1
GCN5L hTAF$_{II}$250
GRIP TFIIB
HAT1 Tip60
HBO1
GCN5
Tip60
CBP/ p300
PCAF
ACTR
Rb
ATM
p53
Stability
DNA Repair
Stability
BRCA1
α-Importin
Nuclear Transport
Cell Signaling
TAFs
TFIIA
TBP
TATA
TFIIH
TFIIF
TFIIB
RNA Pol II
TFIIE
Transcription
Pluripotency
Development
Differentiation of
Neural Stem Cells
BMP, Wnt, Notch
TF
DNA Damage
Histones
NBS1
Deacetylation
Other Sirtuin Substrates
Acetyl CoA Synthetase MEF2
β-catenin p53
E2F1 p130
eNOS PCAF
FoxO PGC-1α
GCN5 PPARγ
Ku70 Rb, p107
LXR Suv39H1
tubulin
Sirtuins
HDAC
NURD
SMRT/ NcoR
Sin3
Known Acetylated Proteins
Acetyl-CoA Synthetase
ACTR
AP endonuclease
AR
ATM
Brm
E2F1, -2, -3
EKLF
ERα
FoxO1, 3, 4
GATA1
HIF-1α
Histones
HMG A1
HSP90
Importin-α
INFR
Ku70
MEF2A
MHG17
Mitochondrial proteins
c-Myb, c-Myc
NF-κB
p21
p53
p73
p300
PCNA
PGC-1α
PR
PTEN
Rb
Runx2
SHP
Smad2
Smad7
SREBP
Stat3
TAF(1)68
TCF
TFIIB
TFIIEβ
TFIIF
TR/RXR
α-tubulin
WRN
HDAC Classes
Class I: HDAC1-3, 8
Class II: HDAC4-7, 9, 10
Class III: SIRT1-7
Class IV: HDACII
Signaling Pathways

Fig. 13

Micro RNAs (miRNAs) are short RNA molecules with an average of 22 nucleotides. They are post-transcriptional regulators that bind to complementary sequences on target mRNA transcripts, usually resulting in translational repression or target degradation and gene silencing. Repression of mRNA may result in its storage for later activation. Degradation cleaves it for recycling amino acids. The human genome may encode well over a thousand miRNA varieties, which may target about 60% of mammalian genes and are abundant in many human cell types. Approximately 50% of miRNA loci are found in close proximity to other miRNAs. These clustered miRNAs are transcribed from single transcription units, although there may be exceptional cases in which individual miRNAs are derived from separate gene promoters. Approximately 40% of miRNA loci are located in the intronic region of non-coding transcripts, whereas about 10% are placed in the exonic region of non-coding transcription units (Tus). miRNAs in protein coding Tus are found in intronic regions, which account for about 40% of all miRNA loci. Some 'mixed' miRNA genes can be assigned to either intronic or exonic miRNA groups, depending on alternative splicing patterns. The transcription of most miRNA genes is mediated by RNA polymerase II (Pol II). A minor group can be transcribed by Pol III.

A range of Pol II-associated transcription factors control miRNA transcription. The pri and pre miRNAs are processed by enzymes transcribed by Pol III. This allows miRNA genes to be elaborately regulated in specific conditions and cell types. This can have either expressive or regenerative effects in the context of carving a pattern of gene expression out of the maze of transcription possibilities. It can also have involutionary effects leading to diseases such as cancer or it can defend against viral attack. The wide variety of miRNAs and siRNAs is quite versatile and works with a multiprotein complex called RISC (RNA Induced Silencing Complex). RISC is activated by incorporating one strand of either miRNA or siRNA. See Figure 14.


Protein-coding gene
MicroRNA gene
Transcription of pri-microRNA
Transcription of mRNA
Pri-microRNA
OR
Drosha
DGCR8
Processing of pri-microRNAs into pre-microRNA
Nucleus
Pre-microRNA
Ran-GTP
Exportin 5
Transport of pre-microRNA into the cytoplasm
Dicer
Loqs/TRBP
Processing of pre-microRNA into small RNA duplexes
Cytoplasm
RISC
An
Delivery of RISC–microRNA complex
mRNA degradation
Translational repression

Antisense RNA is a single-stranded RNA that is complementary to a messenger (mRNA) strand. Antisense RNA inhibits translation of a complementary mRNA by base pairing to it and physically obstructing the translation machinery.

Long non-coding RNAs (long ncRNAs, lncRNA) are non-protein coding transcripts longer than 200 nucleotides. This arbitrary limit distinguishes long ncRNAs from small regulatory RNAs such as (miRNAs), (siRNAs), (piRNAs), (snoRNAs) etc.

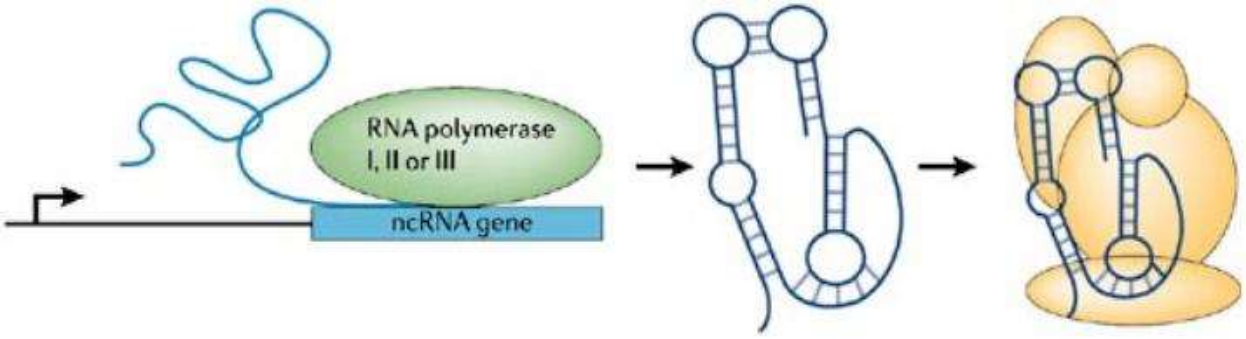
Less than one fifth of transcription across the human genome is associated with protein-coding genes, indicating at least four-times more long non-coding transcription than coding sequences for mRNA. Large-scale sequencing projects have identified over 35,000 non-coding transcripts from over 10,000 distinct loci that bear many signatures of mRNAs, but have little or no open reading frame characteristic of coding sequences. The total number is likely to be much higher and small non coding RNAs are at least as numerous. One of the major findings of the 2007 ENCODE Pilot Project was that "nearly the entire genome may be represented in primary transcripts that extensively overlap and include many non-protein-coding regions."

Most long non-coding sequences are considered likely to be functionally active. Genomic sequences within these transcriptional foci are often shared within a number of different coding and non-coding transcripts in the sense and antisense directions giving rise to a complex hierarchy of overlapping isoforms.

In contrast to small RNAs, long ncRNAs generally lack strong conservation among diverse species suggesting that they may be subject to different selection pressures. Unlike mRNAs, which have to conserve the codon usage (the open reading frame), selection may conserve only short regions of long ncRNAs that are constrained by structure or sequence-specific interactions. Therefore we may see selection act only over small regions of the long ncRNA transcript. Nevertheless, many long ncRNAs still contain strongly conserved elements. For example 19% of some highly conserved elements occur in known introns, and another 32% in unidentified regions. Furthermore, a representative set of human long ncRNAs exhibit small, yet significant, reductions in substitution and insertion/deletion rates indicative of purifying selection that conserve the integrity of the transcript at the levels of sequence, promoter and splicing. This suggests that the poor conservation of lncRNAs may be the result of recent and rapid adaptive selection. Long ncRNAs may be more pliant to evolutionary pressures than protein-coding genes, as evidenced by the existence of many lineage specific lncRNAs. These observations indicate that lncRNAs can play a variety of expressive and regenerative roles in a variety of evolutionary contexts that are fluid. They may also have involutionary influences in some instances.

Fig.14

Fig. 15



The non coding RNA genes can be transcribed by Pol I, II, or III depending on the individual ncRNA. They fold into specific functional structures. They are often incorporated into large complexes (yellow) that contain proteins and sometimes other nucleic acids that together regulate biological functions. (Adapeted from Nature Reviews Molecular Cell Biology, August 2006)

LncRNA continued:
Conserved regions of the human genome that are subject to recent evolutionary change relative to the chimpanzee genome occurs mainly in non-coding regions, many of which are transcribed, including in some cells of the human brain and factors that influence brain development. The observation that many functionally validated RNAs are evolving quickly may result from these sequences having more plastic structure-function constraints, and a great deal of evolutionary innovation is expected to occur in such sequences. RNA transcription is a tightly regulated process. Long ncRNAs can target transcriptional activators or repressors, different components of the transcription reaction including RNA polymerase II and even the DNA double strand itself to regulate gene transcription and expression. In combination these lncRNAs comprise a regulatory network that, including transcription factors, finely control gene expression. The lncRNAs may be expected to display the complementary expressive and regenerative System 4 modes of the evolutionary variant as well as both modes of the involutionary variant.

Ultra- or highly conserved elements of many long ncRNA sequences within the mammalian genome that are both transcribed and fulfill enhancer functions suggest a generalized mechanism that tightly regulates important developmental genes with complex expression patterns during vertebrate growth. They can further modulate the function of transcription factors by several different mechanisms, including functioning as co-regulators, modifying transcription factor activity, or by regulating the association and activity of co-regulators. Local lncRNAs can also recruit transcriptional programs to regulate adjacent protein-coding gene expression.

Long ncRNAs can target general transcription factors required for the RNA Pol II transcription of all coding genes. These general factors include components of the initiation complex that assemble on promoters or that are involved in transcription elongation. Some pathways which bypass specific modes of regulation at individual promoters and that mediate changes directly at the level of initiation and elongation provides a means of quickly affecting global changes in gene expression. They can either initiate or repress transcription.

The ability to quickly mediate global changes is also apparent in the rapid expression of non-coding repetitive sequences. The Short Interspersed Nuclear Elements (SINEs are less than 500 base pairs) in humans are the most abundant mobile elements within the genomes, comprising about 10% of the human genome. These elements are transcribed as ncRNAs by RNA Pol III in response to environmental stresses such as heat shock, where they then bind to RNA Pol II with high affinity and prevent the formation of active pre-initiation complexes. This allows for the broad and rapid repression and shaping of gene expression in response to stress. The abundance and distribution of these and similar repetitive elements throughout the mammalian genome may be partly due to these functional domains being co-opted into other long ncRNAs during evolution, functional repeat sequence domains being a common characteristic of several known long ncRNAs.

Broadly speaking there is a regulatory circuit nested within ncRNAs whereby some may repress general gene expression, while other ncRNAs activate the expression of specific genes. This indicates the selection of specific genes in specific Cell types that code for proteins according the current rapidly changing needs of Organs and Host. Once again the role of Primary Cilia and the orthogonal centrioles is strongly suggested.

Long non-coding RNAs in post-transcriptional regulation
In addition to regulating transcription, ncRNAs also control various aspects of post-transcriptional mRNA processing. Similar to small regulatory RNAs such as micro miRNAs and snoRNAs, these functions often involve complementary base pairing with the target mRNA. The formation of RNA duplexes between complementary ncRNA and mRNA may mask key elements within the mRNA required to bind trans-acting factors, potentially affecting any step in post-transcriptional gene expression including pre-mRNA processing and splicing, transport, translation, and degradation. This can play expressive, regenerative, or involutionary roles.

Long ncRNAs in translation
Long ncRNA may apply regulatory pressures during translation particularly in neurons where the dendritic or axonal translation of mRNA in response to synaptic activity contributes to changes in synaptic plasticity and the remodeling of neuronal networks. RNA Pol III transcribed ncRNAs are expressed in the human central nervous system. Expression is induced in response to synaptic activity and synaptogenesis. It is specifically targeted to dendrites in neurons that shape synaptic connections according to learned experience which can have regenerative meaning to the Host. Sequence complementarity between ncRNA and regions of various neuron-specific mRNAs also suggest a role in targeted translational repression.

Long ncRNAs in epigenetic regulation
Epigenetic modifications, including histone and DNA methylation, histone acetylation and sumoylation, affect many aspects of chromosomal biology, including regulation of large numbers of genes by remodeling broad chromatin domains. While it is known that RNA is an integral component of chromatin, recently the means by which RNA is involved in pathways of chromatin modification is being investigated. Long ncRNAs can induce the expression of homeotic genes that control large netwrorks of other genes essential to programmed development in concert. Strong epigenetic mechanisms are thought to underlie the embryonic expression profiles of the Hox genes that persist throughout human development. The human Hox genes are associated with hundreds of ncRNAs that are sequentially expressed in human development and define chromatin domains with different histone methylation patterns and RNA polymerase accessibility needed to transcribe DNA. The prevalence of long ncRNAs associated with protein coding genes can contribute to localized patterns of chromatin modification that regulate gene expression during development. This can also have a role in disease. For example, most protein-coding genes have antisense partners. The miss-expression of the associated antisense ncRNAs may silence the tumour suppressor gene and contribute to cancer.

Eukaryotic Gene Regulation: Summary of Above Key Points:

Eukaryotic gene expression can be regulated at a variety of points along the pathway of gene expression, including transcription, processing, mRNA stability, and translation into protein.

- Many pre mRNA transcripts can undergo differential splicing, producing different mRNA molecules encoding differences in the polypeptide sequences of protein.
- Full, correct transcription requires the concerted activity of promoter sites and at least one enhancer. Enhancers increase transcription of a gene over basal level, and they regulate tissue-specific gene transcription.
- Enhancers are bound by specialized transcription factors that enhance transcription.
- Transcription factor activity in a cell can be regulated by whether or not the factor is synthesized in the cell, initiated by environmental signals, or by signals (such as hormones) from other cells.
- Transcription factors have one functional domain for DNA binding, and one for transcription activation. Transcription factors can be classified according to the structure of their DNA binding domains. These include zinc finger proteins, helix-turn-helix proteins, leucine zipper proteins, helix-loop-helix proteins, and steroid receptors.

Regulation of transcription controls when and where transcription occurs and how much RNA is created. Transcription of a gene by RNA Polymerase can be regulated by at least five mechanisms:

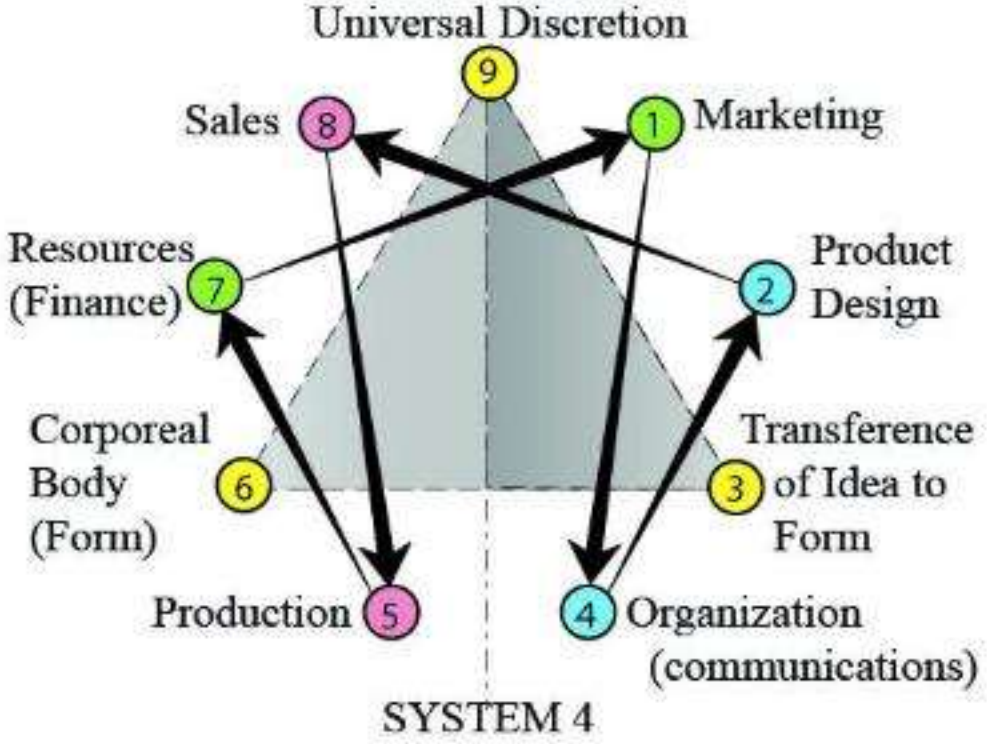
- **Specificity factors** alter the specificity of RNA polymerase for a given promoter or set of promoters upstream of specific genes, making it more or less likely to bind to them
- **Represors** bind to non-coding sequences on the DNA strand that are close to or overlapping the promoter region, impeding RNA polymerase's progress along the strand, thus impeding the expression of the gene. This includes epigenetic factors such as DNA methylation and histone tail modifications that can repress (or actively facilitate) transcription.
- **General Transcription Factors** position RNA polymerase at the start of a protein-coding sequence and then release the polymerase to transcribe the RNA. As transcription finishes the RNA 3' end is cleaved and polyadenylated by adding a stretch that only has adenosine monophosphate (A) nucleotides. In some genes, proteins cleaved from preRNA may add a poly(A) tail at one of several possible sites to produce more than one transcript from a single gene, similar to alternative splicing. The poly(A) tail is important for the nuclear export, translation, and stability of mRNA. The tail is shortened over time, and, when it is short enough, the mRNA is enzymatically degraded. In a few cell types, mRNAs with short poly(A) tails are stored for later activation by re-polyadenylation in the cytosol.
- **Activators** enhance the interaction between RNA polymerase and a particular promoter, encouraging the expression of the gene. Activators do this by increasing the attraction of RNA polymerase for the promoter, through interactions with subunits of the RNA polymerase or indirectly by changing the structure of the DNA (as in the case of epigenetic factors).
- **Enhancers** are sites on the DNA helix that are bound to by activators in order to loop the DNA bringing a specific promoter to the initiation complex in eukaryotes.

Both modes of System 4 are implicated in the above processes in both the evolutionary and involutionary variants depending on circumstances.

Transcriptional Regulation and System 4:

In conjunction with RNA transcription and processing the amount of protein translated must be regulated. It is one thing to design a product and the manufacturing apparatus required to make it and quite another to produce just enough to meet market demands. The former is an Engineering Design function (Term 2). The latter is a Sales function (Term 8) based on sales forecasts in the light of prior membrane Marketing information (Term 1) and the signaled Organizational capacity available as it relates to demand (Term 4). The Production function (Term 5) can then proceed according to available production capacity consistent with Sales input (Term 8) to meet immediate market demand as well as it can. This can only be accomplished according to the distributed Energy Resources (Term 7 Finance) budgeted to each specific Cell type in the Organs of the Host by Universal Terms.

Engineering (T2) and Sales (T8) must work in close cooperation in the nucleus to accomplish a balanced result. The Primary Universal Set transforms from T9 to a regenerative alignment T8R with the expressive Particular T8E in Step 3 of each Cycle while the Secondary Universal Set transforms from T6 to an Expressive alignment T2E with the regenerative Particular T2R in Step 4 of each Cycle. The Universal Term interfaces are detailed in other articles and will be discussed more later here.



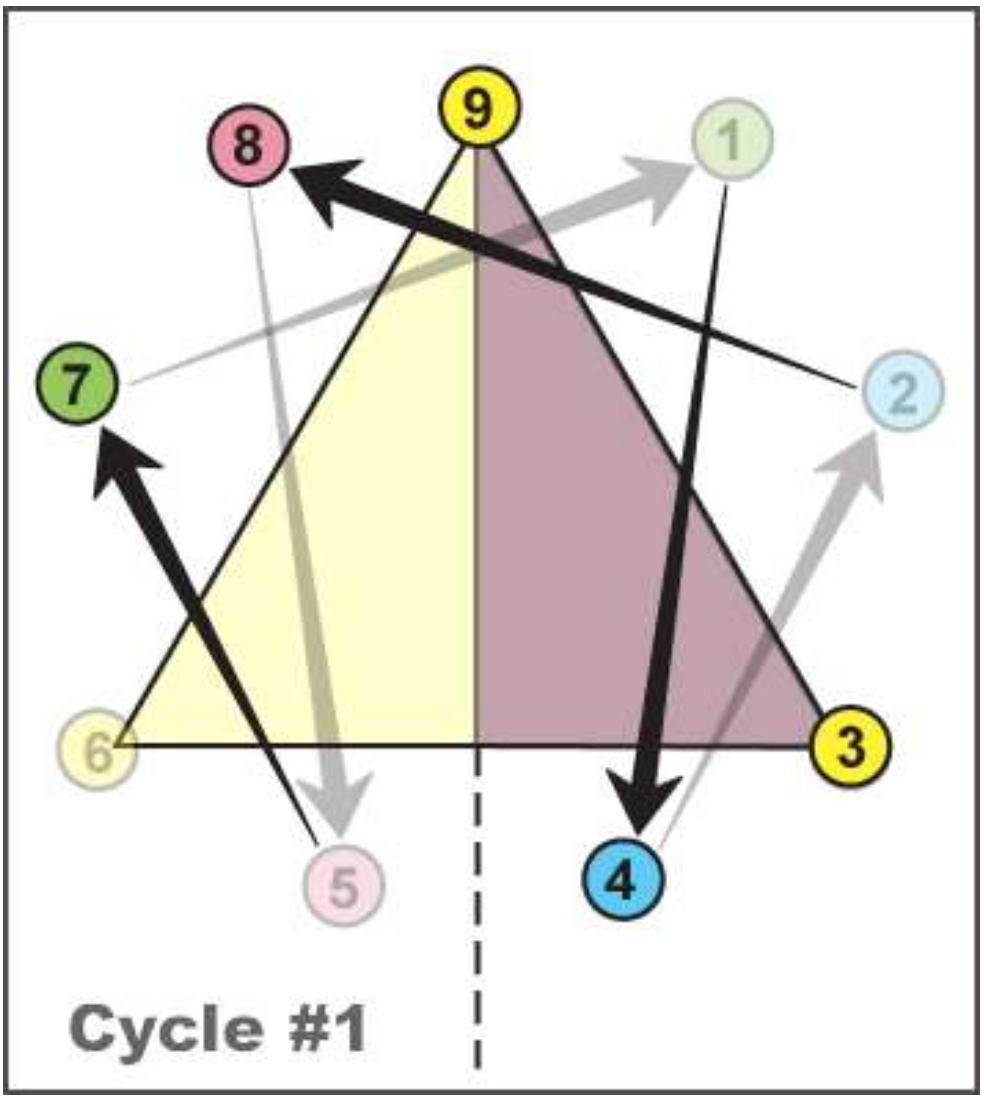
The three Particular Sets are illustrated by red, green and blue circles such that Terms 8, 7 and 4 synchronously alternate with Terms 1, 2 and 5. The Terms alternate between expressive and regenerative modes as shown in the Figure 18 chart.

The Primary Universal Term UT9 defines a subjective to objective axis. UT9 transforms to UT8R in Step 3 of each cycle and shifts back after Step 4 to begin Step 1 of the next 4 Step cycle.

The Secondary Universal Term UT3 transforms to UT6 in Step 2 of each Cycle. In Step 4 it inverts to a universal UT2E expressive mode of Product Design for the whole body then it shifts back to UT3 next cycle. Together with UT8R this distributes resources to a priority of needs.

Fig. 16

Three Particular Sets of System 4 Terms transform through the six Term sequence one step apart in each pathway and there may be any number of similar parallel pathways. Each Particular Set transforms through seven Expressive Term modes alternating with five Regenerative Term modes. The Particular Sales term T8E is always in the expressive mode. Reconciliation of the expressive and regenerative modes of System 4 is vital to sustaining a balance between causal input derived from past events and an anticipated future result. This is essential to the overall integration of events in space and time in the intimate relationship between Cells, Organs and Host. The expressive and regenerative modes span space and time. The pattern is designated in Figure 18.



There is a lot of reciprocal cross talk between the six domains of activity as the six term sequence 1, 4, 2, 8, 5, 7 keeps repeating in each Cell as it relates to Organs and Host. As more empirical evidence is accumulating it indicates this intimate triadic relationship is moderated by primary cilia and the orthogonal centrioles consistent with System 4. The primary cilia and centrioles have only recently received a lot of research attention. We shall return to this shortly. Figures 16, 17 and 18 illustrate the pattern of System 4.

The two Universal Sets go through their transform sequences in four Particular Steps that define each Cycle. Since there are three synchronous Particular Sets transforming one Step apart all the expressive and regenerative modes of the six Particular Terms occur in each Cycle and must be mutually reconciled between different sets. However it takes twelve steps for each Particular Set in each pathway to transform through seven expressive and five regenerative modes so that three Cyces are needed to complete each pathway. This can be seen by examining Figures 17 and 18.

Fig. 17

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 other website articles the role of calcium signaling (T4R) initiated by certain membrane processes (T1R) has been implicated in regulating the interplay between expressive and regenerative signaling modes. (Keep in mind that System 4 elaborates in levels within itself because of how the four levels begin to break out again within each of the six Particular domains.)

The production of protein (T5R) synthesized at ribosomes into the cytosol is generally for regenerative cell maintenance functions determined by Engineering (T2R) as moderated by the Primary Universal regenerative term UT8R in conjunction with the Secondary Universal expressive term UT2E that together distribute energy resources according to a priority of needs. This includes the specification of ncRNAs that synthesize regulatory transcription protein factors in the cytosol that are imported back into the nucleus. The simple availability of free ribosomes, tRNAs and amino acids in the cytosol places an upper Production T5R limit on this process. Otherwise the quantity of protein coding mRNA that is transcribed in the nucleus for export from the cell is a Sales T8E function. The specification of the gene pattern to be transcribed is an expressive Engineering Product Design function T2E. Only the demand for a specific amount of mRNA to be transcribed for protein export is a Sales expressive function T8E but this does influence the T5R Production capacity and T2R Design activity to increase or decrease Production capacity to match export demand, just as in a corporation.

Sales and Engineering must work in close cooperation in the nucleus to determine the kind and amount of transcription factors and other regulatory proteins, the number of ribosomes needed and so on. All of this activity in each cell is constrained by the available energy resources allotted to each cell. This energy distribution pattern is regulated by the two Universal Sets working in concert.

The T5R Production Maintenance Department synthesizes protein for cell operation and maintenance at Ribosomes in the cytosol. The T5E Production assembly line translates protein at ribosomes that discharge polypeptides strands into the endoplasmic reticulum (ER) where it is further processed on its journey through the sacs of the Golgi apparatus then packaged in vesicles for export from the cell. Production T5E export supply strives to balance Sale T8E demand. When the Secondary Universal Set transforms to T2E in alignment with all Particular Terms T2R in Step 4 this influences the Engineering Design function in every cell to adjust Production capacity T5R accordingly.

The regenerative Primary Universal Term UT8R has an asymmetrical subjective bias that distributes available energy resources to organs and cells throughout the body according to a budgeted priority of needs. This also relates to the Secondary Universal Expressive pattern T2E in Step 4 of each Cycle that conditions the Particular regenerative Engineering of Cell facilities T2R such that the cells involved can meet anticipated demand consistent with distributed energy resources. (Note that some organs such as heart, pancreas and liver have an asymmetrical bias as do the functional domains of the cerebral hemispheres.)

Some ER processed protein is modified to become signal receptors and membrane transport channels with receptor components added. They are included in export vesicle membranes that become integrated into plasma membrane processes (T1) that reflect the capacity of the cell to respond to its environment as needed. This can regulate the capacity of the cell either up or down to suit changing circumstances consistent with the effect of the Universal T2E Term on the Particular T2R Terms in Step 4 of each Cycle.

The type, quantity and location of receptors and transport channels relate the internal capacity of the cell to the external environment. Under specific ion concentrations and /or ligand binding this initiates phosphorylation events internal to the membrane in Term T1. If conditions are right this can initiate signaling cascades (T4) that may dock on transcription factors and co-factors at DNA promoter and enhancer sites of genes to specify a transcription pattern of RNA (T2). As discussed above this can adjust the expressive capacity of the cell according to Sales demands (T8E) specific to each cell. Regenerative needs on the supply side seek a balance with expressive demands.

Synchronous Terms of Universal Sets (U) and Particular Sets (S) are in each vertical Step. The transform sequence and mode Expressive (E) or Regenerative (R) are in the rows. The 9x3 structure of centrioles channel the 3 Cycles.

Summary of System 4 as it relates to Translation of Protein:

This summary review of the System 4 pattern of operation outlines in broad strokes the structural dynamics of how the Cell operates with respect to Organs and Host. This much simplified description provides an initial indication of how the maze of transcription and other factors work together although the full description is much more complex.

For example one can see from the Figure 18 chart that each Cycle has one Expressive and one Regenerative Production mode (T5) in Steps 2 and 4 respectively. Translating mRNA into protein is illustrated in Figure 19, however the detailed process is an elaboration of System 4 within itself as it relates to the whole cell which is an elaboration within itself with respect to the overall relationship between Cell, Organs and Host. The interpretation of the System 4 Terms is context dependent. This property of the System makes it possible to employ System 4 in separate hierarchical stages rather than attempt to decipher and employ the prohibitively complex higher Systems. How this can work in practice is illustrated in Figure 19.

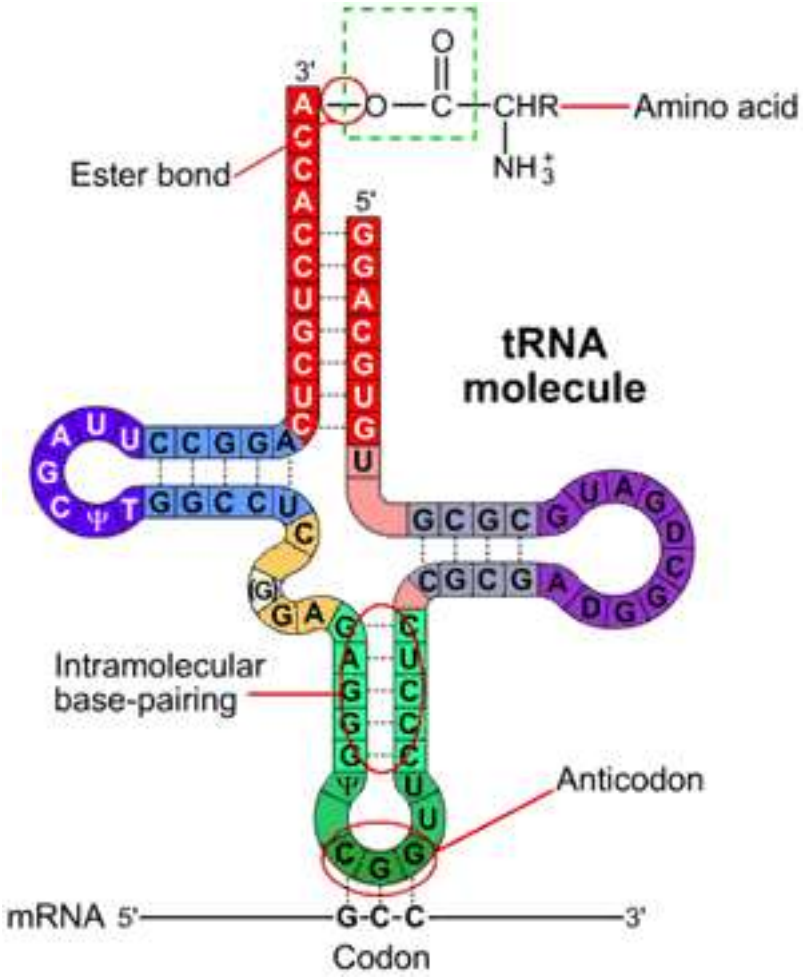
Figure 19 shows how System 4 elaborates in a self-similar way within the more general context of the Production function (T5) for the whole cell. Identifying each of the three nucleotides in each mRNA codon as illustrated in Figure 19 is an Expressive (T5E) function while matching that codon with its anti-codon in transfer tRNA concerns the Regenerative production of protein (T5R) regardless of whether it relates internally to the cell or externally for the regenerative maintenance of the whole body in this context. (The male human can only express protein externally via sperm along with genes in sexual union thus fertilizing the female to regenerate a new human infant.) Ribosomes are all the same and work the same way regardless of whether they are free ribosomes in the cytosol or attached to the ER and translating protein for export from the cell. The point is that each Cycle of System 4 matches up one of the nucleotides of mRNA with the appropriate member of the three member anti-codon sequence in the tRNA, so in this context each match is regenerative.

It thus takes three Cycles to match up each codon with the tRNA anti-codon that brings the correct amino acid to add to the growing polypeptide chain. System 4 reads the expressive code and translates it one nucleotide sequence at a time. In each Cycle the three Particular Sets must reconcile expressive and regenerative modes of synchronous Terms. This serves to identify and match each member of each three nucleotide codon with its anti-codon in the ongoing three Cycle repeats.

Once initiated the transcription of RNA from DNA works in a similar way. In this context identifying each of the three nucleotides in each DNA codon is an Expressive (T5E) function while matching up each complementary nucleotide concerns the Regenerative production of RNA (T5R). In this context the Polymerase replaces the role of the Ribosome. The Polymerase that transcribes the RNA is the production machine operated by a host of transcription factor workers and co-workers. The free nucleotides that gravitate to form the RNA strand, link by link do not require a transfer tRNA to bring them to each bonding site as in the translation of protein. There are only four kinds of nucleotides required to make RNA and they can only match up in two pair combinations. They are presumably present in sufficient quantity unless access is repressed or hindered in some way. In this respect it is a simpler process than having to select from twenty amino acids which one to add next. Twenty variations of tRNA are needed to assemble twenty amino acids into the polypeptide protein strand, each one specific for each amino acid codon.

The empirical evidence reviewed previously and the extensive variety of non-coding factors within each cell that influence transcription and translation is regulated by the structural dynamics of System 4. There are related factors that distinguish tissue specific cells in the body's various organs in a hierarchical manner. This process is regulated by the primary cilia and the orthogonal centrioles that serve as System 4 channels to facilitate the structural distribution of the available energy resources from fetal development to adult maintenance. Some of these related factors will be reviewed next before we return to see how System 4 works its magic in more detail. These factors include Hox genes, and related signaling pathways such as Wnt, Hedgehog, Inversin, PDGF, Notch, Hippo and others that have specific relationships with primary cilia and the orthogonal centrioles.

Fig. 19


3'
5'
Ester bond
Amino acid
tRNA molecule
Intramolecular base-pairing
Anticodon
mRNA 5'
3'
Codon

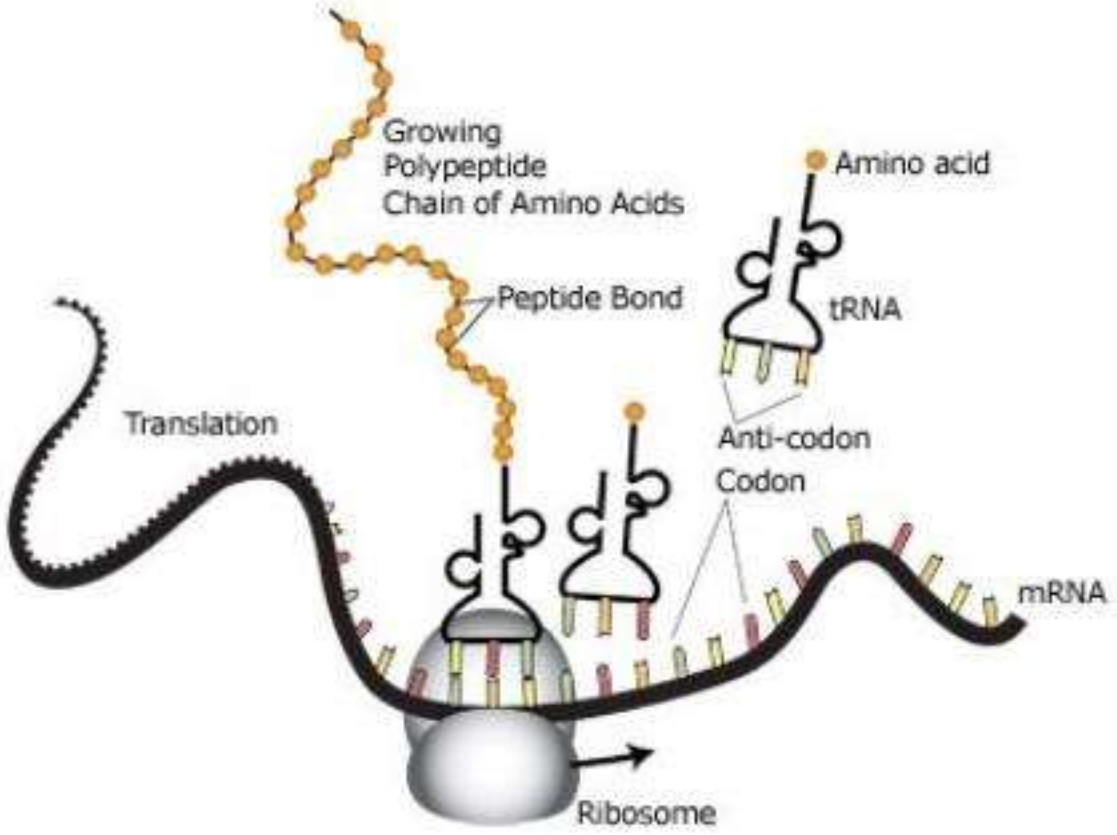


Image adapted from: National Human Genome Research Institute.

Hox Genes:

Hox genes are a group of related genes that determine the basic structure of an organism. They are critical for the proper placement of segment structures such as limbs and organs of all animals during early embryonic development. Hox genes are defined as having a DNA sequence known as the homeobox and they are located in gene clusters on the genome. Their expression pattern follows an axis from head to tail in a sequence corresponding to their gene locations in the Hox gene cluster.

The homeobox is a 180 nucleotide long DNA sequence that encodes a 60 amino acid long protein domain known as the homeodomain. The products of Hox genes are Hox protein transcription factors. The homeodomain part of Hox proteins can bind to specific enhancer sequences on DNA where they either activate or repress genes. The same Hox protein can act as a repressor at one gene and an activator at another.

Not all Hox genes give homeotic mutant phenotypes and not all genes that give homeotic mutant phenotypes encode homeodomain proteins although they generally do in humans. The homeobox is a sequence motif in genes, while "homeotic" is a functional description for genes that scaffold structures or developmental patterns. However the terminology Hox genes is generally accepted for mammals and humans. The homeodomain protein motif is highly conserved across vast evolutionary distances. For example Hox proteins with identical homeodomains are assumed to have identical DNA-binding properties (unless additional sequences are known to influence that). A fly can function perfectly well with a chicken Hox protein in place of its own despite having a last common ancestor that lived over 670 million years ago.

Most insects (and other segmental animals) contain all the segment identity genes in one large complex called HOM-C. However the segment identity genes are chromosomally located in two gene complexes rather than one in the fruit fly indicating the complex may have split during its evolution. The Antennapedia complex controls head and thorax segment identities. The Bithorax complex controls abdominal segment identities. Humans have four hox gene clusters on different chromosomes.

Consider the gene wingless in the developing fruit fly illustrated in Figure 20(b). It is a member of the Wnt family of genes associated with primary cilia. In the early embryonic development of the fruit fly wingless is expressed across almost the entire embryo in alternating stripes three cells separated from the egg. This pattern is lost by the time the organism develops into a larva, but wingless is still expressed in a variety of tissues such as patches of tissue that will develop into the adult wings. The spatiotemporal pattern of wingless gene expression is determined by a network of regulatory interactions consisting of the effects of many different genes such as even-skipped and Krüppel in Figure 20(b).

In conventional logic the question of what causes spatial and temporal differences in the expression of single genes depends on previous expression patterns. This introduces a regressive problem explaining the past causes of the first differences in gene expression, known as symmetry breaking. The question does not arise if the System is acknowledged as an eternally evolving pattern of change that never changes. In the case of embryonic fruit fly development, the genes nanos and bicoid are asymmetrically expressed in the egg because maternal cells deposit mRNA for these genes in the poles of the egg before it is laid. This anticipates its future regenerative development.

Figure 20(a) illustrates that the linear order of the genes within a cluster is directly correlated to the order of the regions they affect as well as the timing in which they are affected. As a general rule genes expressed toward the tail end tend to repress genes that have been expressed at the head end. Gene expression is hierarchical.

Human Hox Genes:

Human Hox genes occur in four clusters. Hox A, B, C and D are on chromosomes 7, 17, 12,and 2 respectively. Thirteen Hox genes are duplicated and most appear in most clusters. Although these vertebrate genes are duplicates of the same genes seen in invertebrate animals, the four copies are not identical. Each copy has accumulated its own unique mutations over time, producing proteins with distinct functions. Some have been deleted entirely or duplicated again in certain vertebrate groups. For example, Hox A and Hox D are involved in the segment identity along the limb axis. Hox expression in the limb has two phases, an early wave of expression for the arm and a late wave for the digits, which involves Hox D 8 to 13. HoxD13 is not found in some early vertebrates. Figure 21 illustrates the relationship between Hox genes in mammals including humans as compared to insects.

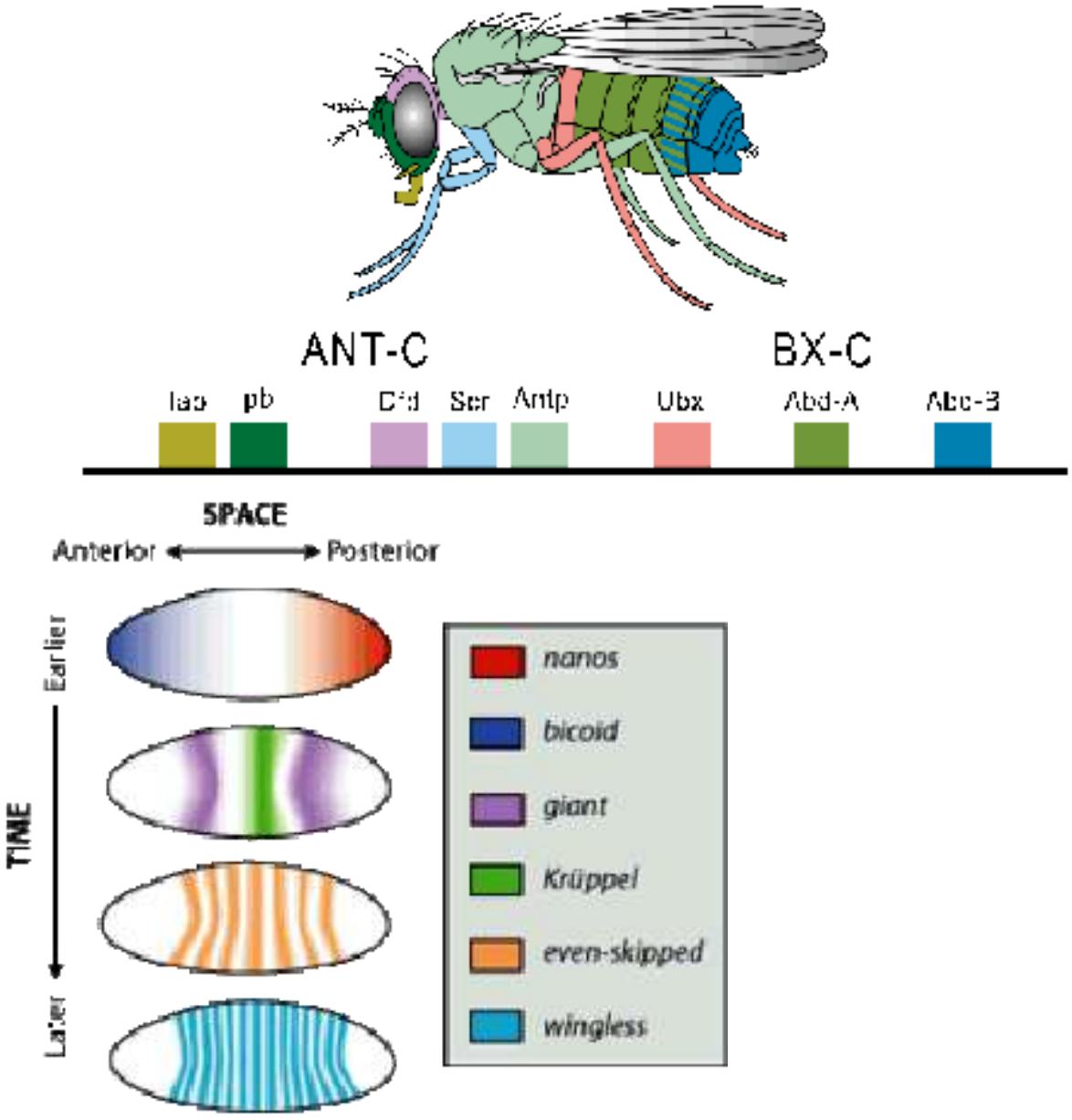
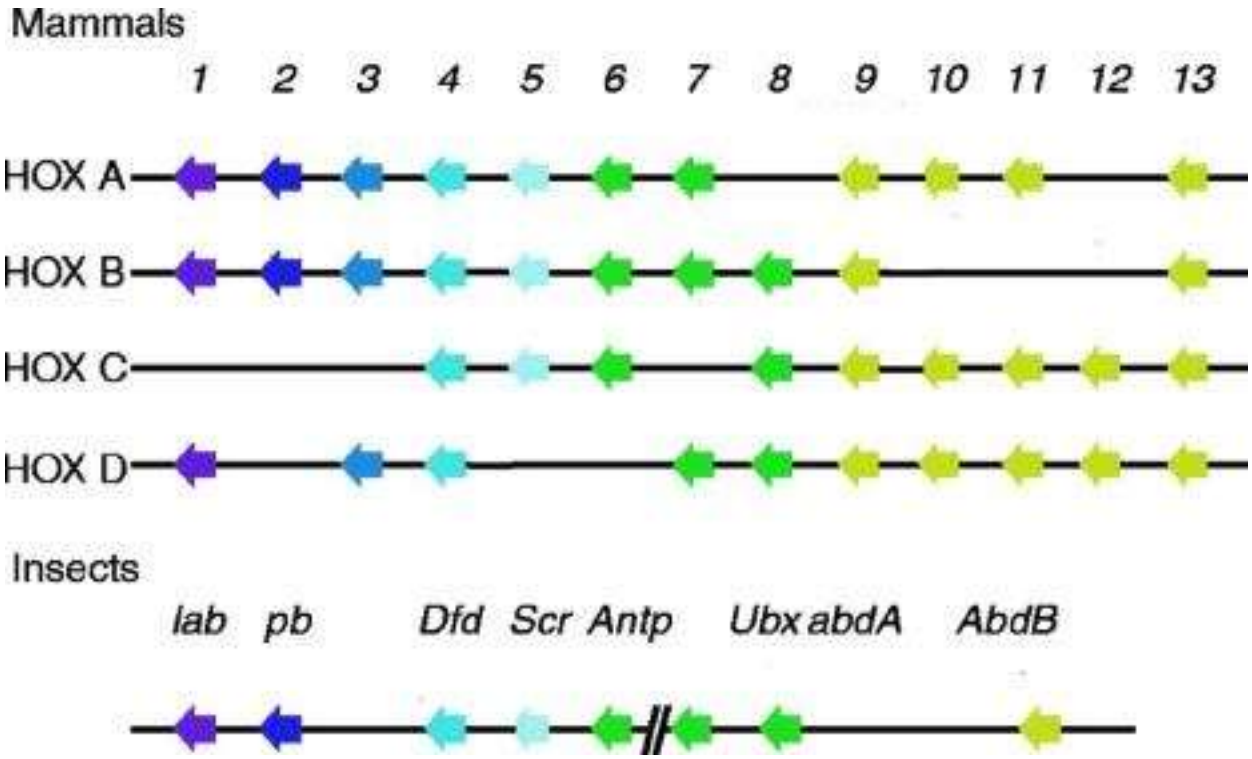

ANT-C
BX-C
lab
pb
Dfd
Scr
Antp
Ubx
Abd-A
Abd-B
SPACE
Anterior
Posterior
TIME
Earlier
Later
nanos
bicoid
giant
Krüppel
even-skipped
wingless

Fig. 20a



Other Factors Influencing Human Development:

MicroRNA strands located in Hox clusters have been shown to inhibit more anterior Hox genes ("posterior prevalence phenomenon"), possibly to fine tune its expression pattern. Non-coding (ncRNA) is also abundant in Hox clusters. In humans, several hundred ncRNAs may be present. One of these, called HOTAIR, is transcribed from the HoxC cluster and inhibits late HoxD genes by binding to Polycomb-group proteins (PRC2). They are a family of proteins that can remodel chromatin such that epigenetic silencing of Hox genes takes place during embryonic development.

In higher animals and humans, retinoic acid (a metabolite of vitamin A) helps to regulate differential expression of Hox genes along the anteroposterior axis. Genes in the 3' ends of Hox clusters are induced by retinoic acid resulting in expression domains that extend more anteriorly in the body compared to 5' end Hox genes that are not induced by retinoic acid resulting in expression domains that remain more posterior. Recent studies demonstrated that stromal (stem) cells isolated from adult bone marrow can differentiate into neuronal cells. Sonic hedgehog (Shh) and retinoic acid (RA), which are signaling molecules secreted from tissues in the vicinity of peripheral sensory ganglia during embryogenesis, exert synergistic effects on neural-competent stem cells to express a comprehensive set of glutamatergic sensory neuron markers. Application of Shh or RA alone has little or no effect indicating their joint synergy as sensory competence factors for adult pluripotent cells. This suggests that they relate in complementary expressive and regenerative modes. Hedgehog signaling is regulated by primary cilia.

Fig. 21

Mammalian Hox genes are expressed sequentially from the head along the dorsal axis of the neural tube, neural crest, paraxial mesoderm and surface ectoderm and in derivatives of these tissues.

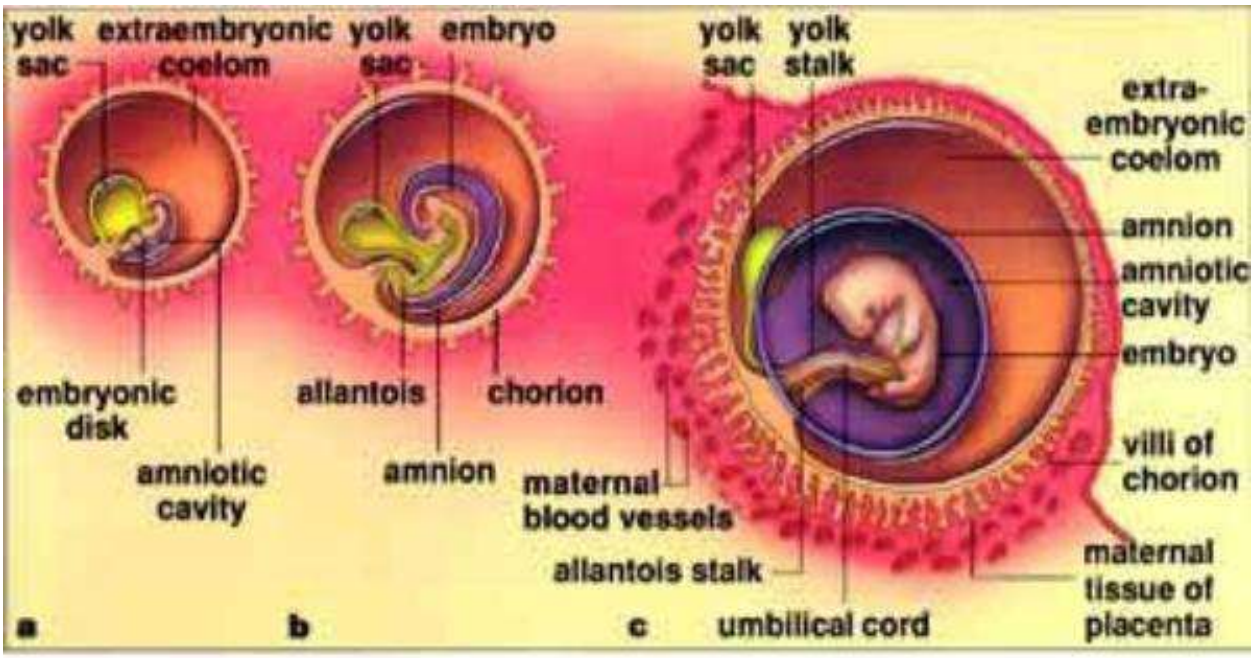
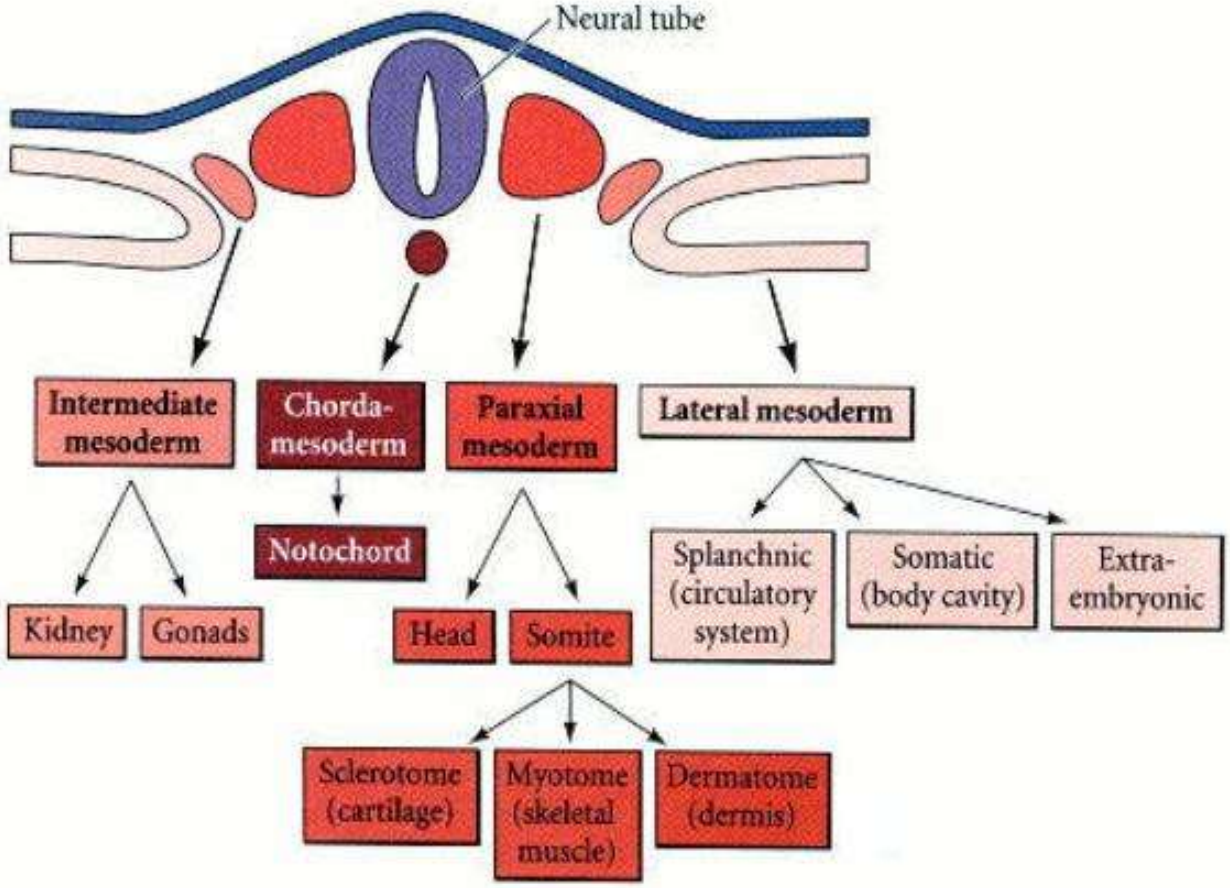

yolk sac
extraembryonic coelom
yolk sac
embryo
yolk sac
yolk stalk
extra-embryonic coelom
amnion
amniotic cavity
embryo
villi of chorion
maternal tissue of placenta
embryonic disk
amniotic cavity
allantois
amnion
chorion
maternal blood vessels
allantois stalk
umbilical cord
a
b
c

Fig. 22


Neural tube
Intermediate mesoderm
Chorda-mesoderm
Paraxial mesoderm
Lateral mesoderm
Kidney
Gonads
Notochord
Head
Somite
Splanchnic (circulatory system)
Somatic (body cavity)
Extra-embryonic
Sclerotome (cartilage)
Myotome (skeletal muscle)
Dermatome (dermis)

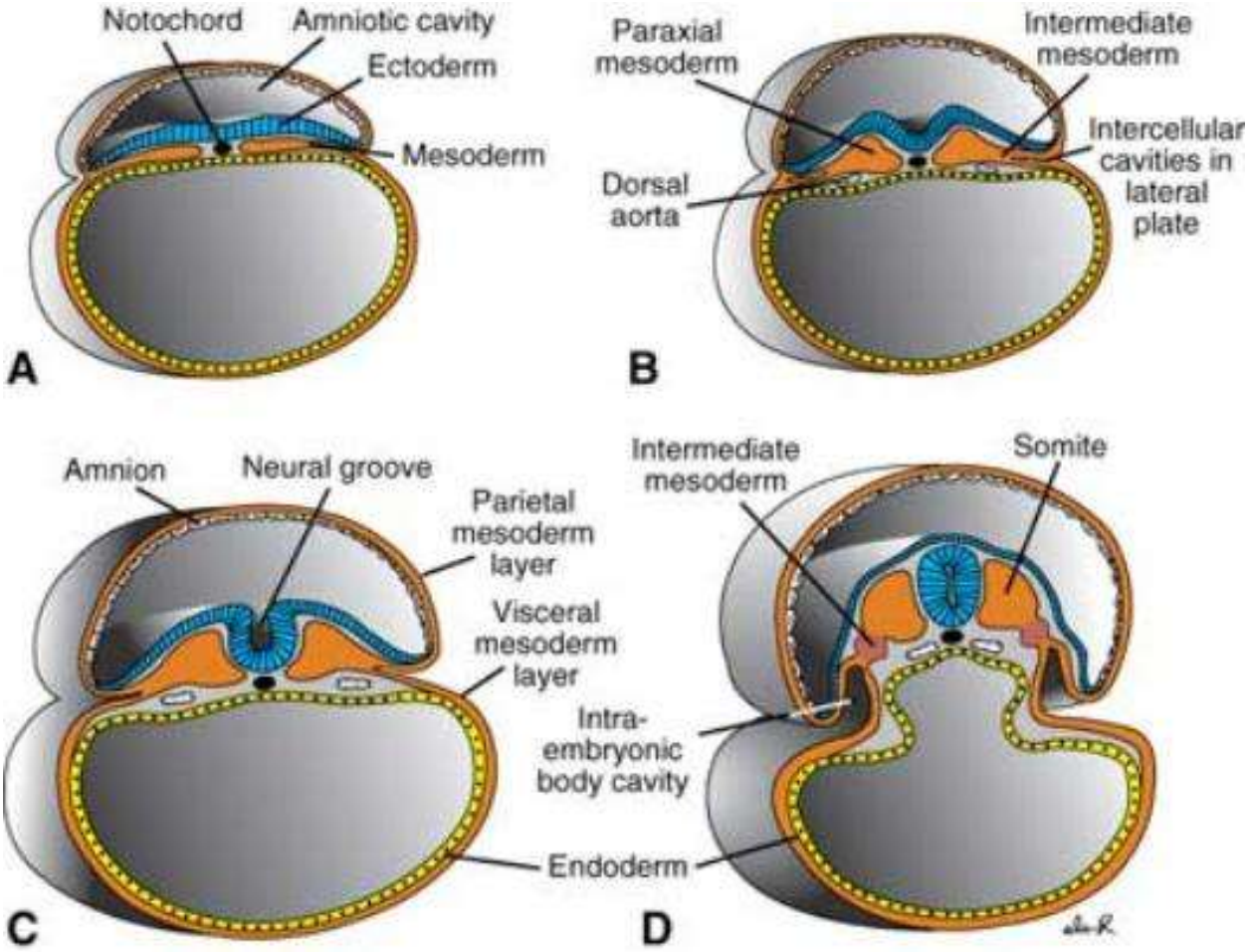


Fig. 23

Fig. 24

Fig. 20b

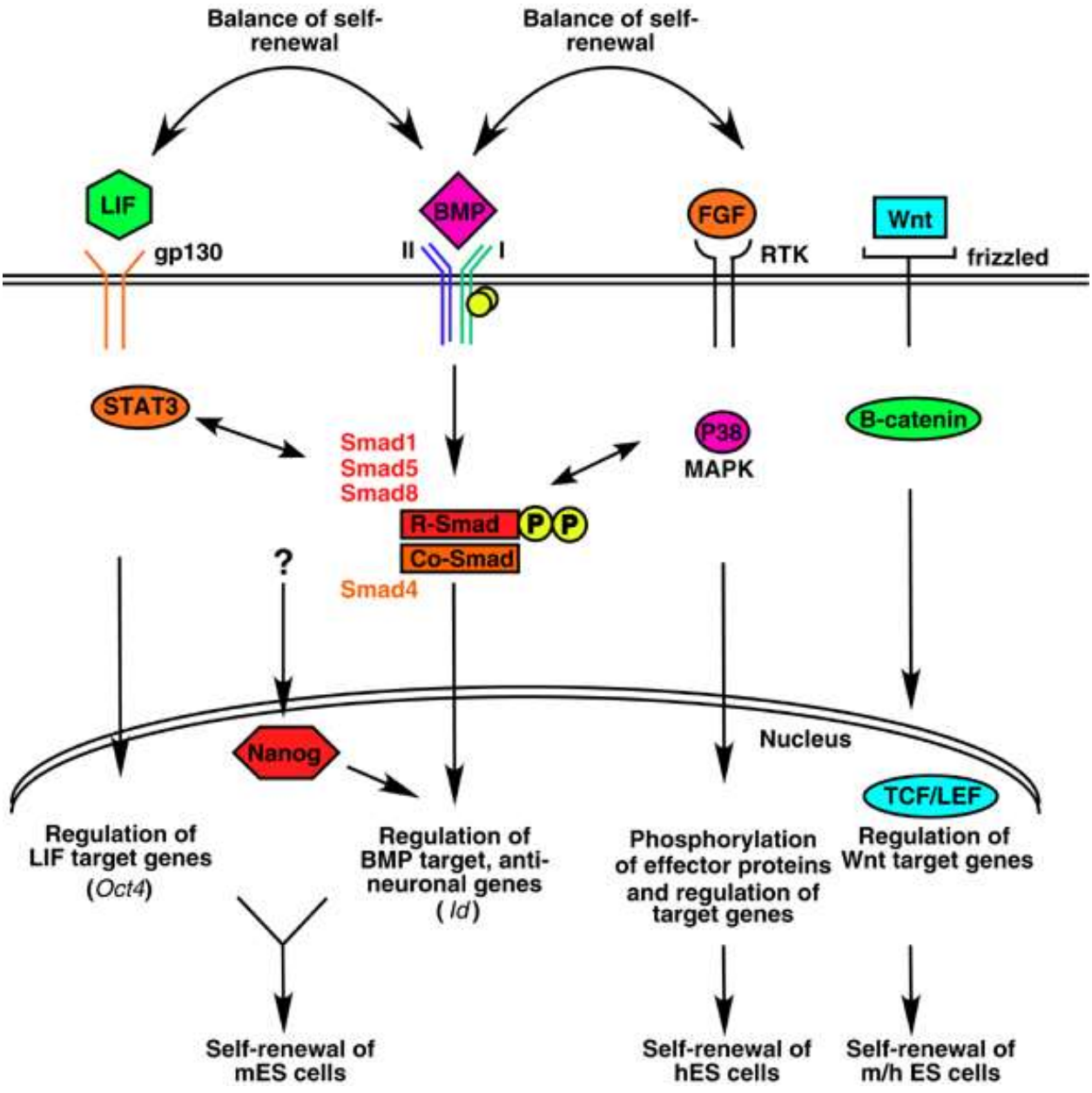

Balance of self-renewal
Balance of self-renewal
LIF
gp130
BMP
II
I
FGF
RTK
Wnt
frizzled
STAT3
Smad1
Smad5
Smad8
P38
MAPK
B-catenin
R-Smad
P
P
Co-Smad
Smad4
?
Nanog
Nucleus
TCF/LEF
Regulation of LIF target genes (Oct4)
Regulation of BMP target, anti-neuronal genes (Id)
Phosphorylation of effector proteins and regulation of target genes
Regulation of Wnt target genes
Self-renewal of mES cells
Self-renewal of hES cells
Self-renewal of m/h ES cells

Fig. 25

Notes relevant to Figure 25 and Primary Cilia:

Some signaling pathways regulating mouse embryonic stem cells (mES), human embryonic stem cells (hES) and both together (m/h ES) are shown in simplified schematics of the BMP, LIF, FGF and Wnt signaling pathways to control stem cell self-renewal versus differentiation. Fibroblast growth factor (FGF) binding induces receptor tyrosine kinase (RTK) to activate a plethora of signaling pathways involved with cell growth, differentiation and functions important for normal development, tissue maintenance and wound repair. In addition to cell surface signaling, some FGF:FGF receptor complexes are trans-located to the nucleus where they signal gene expression. Recent work suggests that some FGF isoforms may function as nuclear signaling factors without ever being secreted, indicating the regenerative mode.

FGF signalling plays a fundamental and highly conserved role in the regulation of primary cilia length in multiple tissues. Loss of Fgfr1 signalling down-regulates expression of two ciliogenic transcription factors, foxj1 and rfx2, and of the intraflagellar transport (IFT) gene ift88 (also known as polaris), indicating that FGF signalling mediates primary cilia length through an Fgf8/Fgf24–>Fgfr1–>intraflagellar transport pathway. Intraflagellar transport (IFT) both assembles and deassembles primary cilia as well as relocating signal receptors and channels.

In the embryonic neural tube, multiple signaling pathways work in concert to create functional neuronal circuits in the adult spinal cord. In the ventral neural tube, Sonic hedgehog (Shh) acts as a graded morphogen to specify motor neurons necessary for movement. In the dorsal neural tube. Bone morphogenetic protein (BMP) and Wnt signals cooperate to specify neurons involved in sensation. Sensory and motor regulation result from the Term transformations of System 4. These signaling pathways are directly related to primary cilia in vertebrates. Deletion of the gene encoding the BMP type 1 receptor (Acvr1) inhibits the appearance of nodal primary cilia in the early development stages of the mammalian embryo, which results in defects in leftward fluid flow and, thus, abnormalities in left-right patterning. System 4 is clearly involved.

Smoothened (Smo), Patched (Ptch), Frizzled receptors, and Gli family transcription factors which are effectors of Hh signaling in conjunction with other signaling families all localize to the primary cilium and traffic dynamically in and out of the organelle in a Hedgehog (Hh) dependent manner.
The two centrioles that are formed from nine sets of microtubules (red tubes) which are triplet at the proximal ends and doublet at the distal ends of centrioles. The two centrioles are attached to one another at their proximal ends by a flexible linker (green ribbons). Surrounding the proximal ends of each centriole is a matrix of proteins called the pericentriolar material (PCM). It is a site of microtubule nucleation as well as procentriole assembly (yellow ribbons representing protein). The mother centriole is slightly longer and possesses two sets of appendages (distal and sub-distal drawn as orange sticks and red cones, respectively). PLK4 localizes to the proximal ends of both centrioles and the distal end of the mother centriole. From *Sillibourne and Bornens Cell Division 2010 5:*

Some Primary Cilium and Centrosome Details:

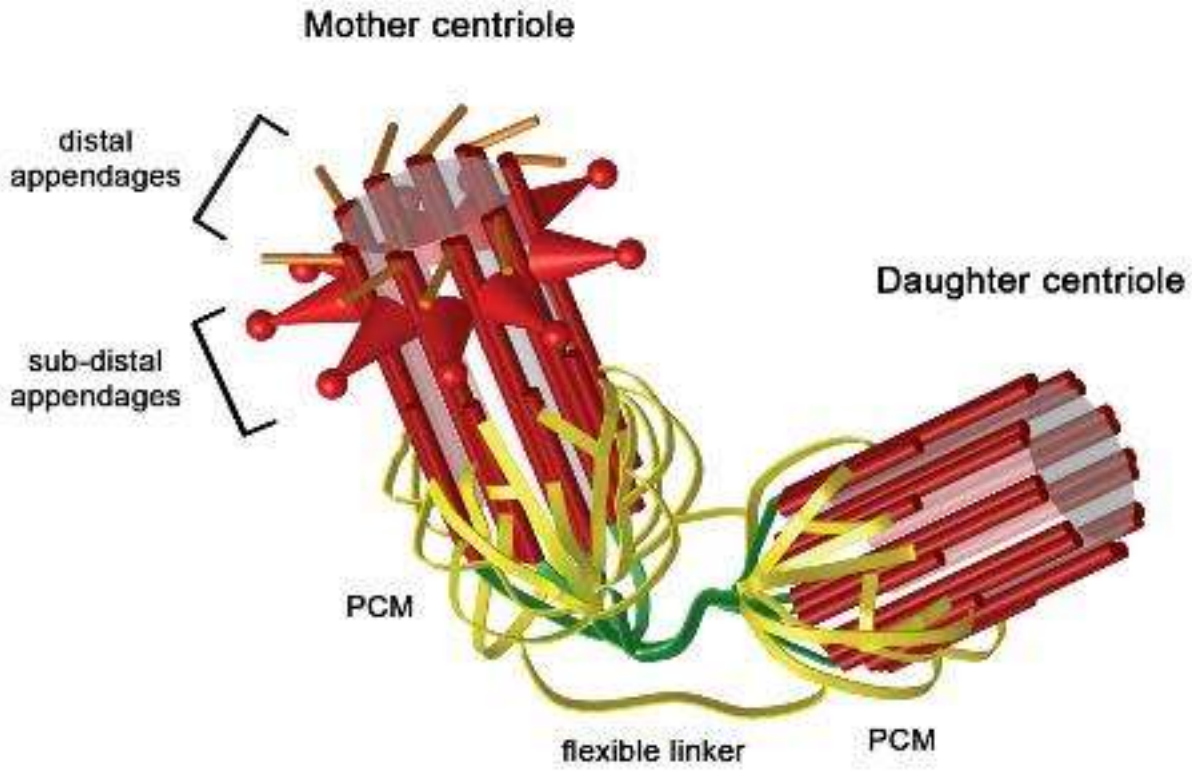

Mother centriole
distal appendages
sub-distal appendages
Daughter centriole
PCM
flexible linker
PCM

Fig 26

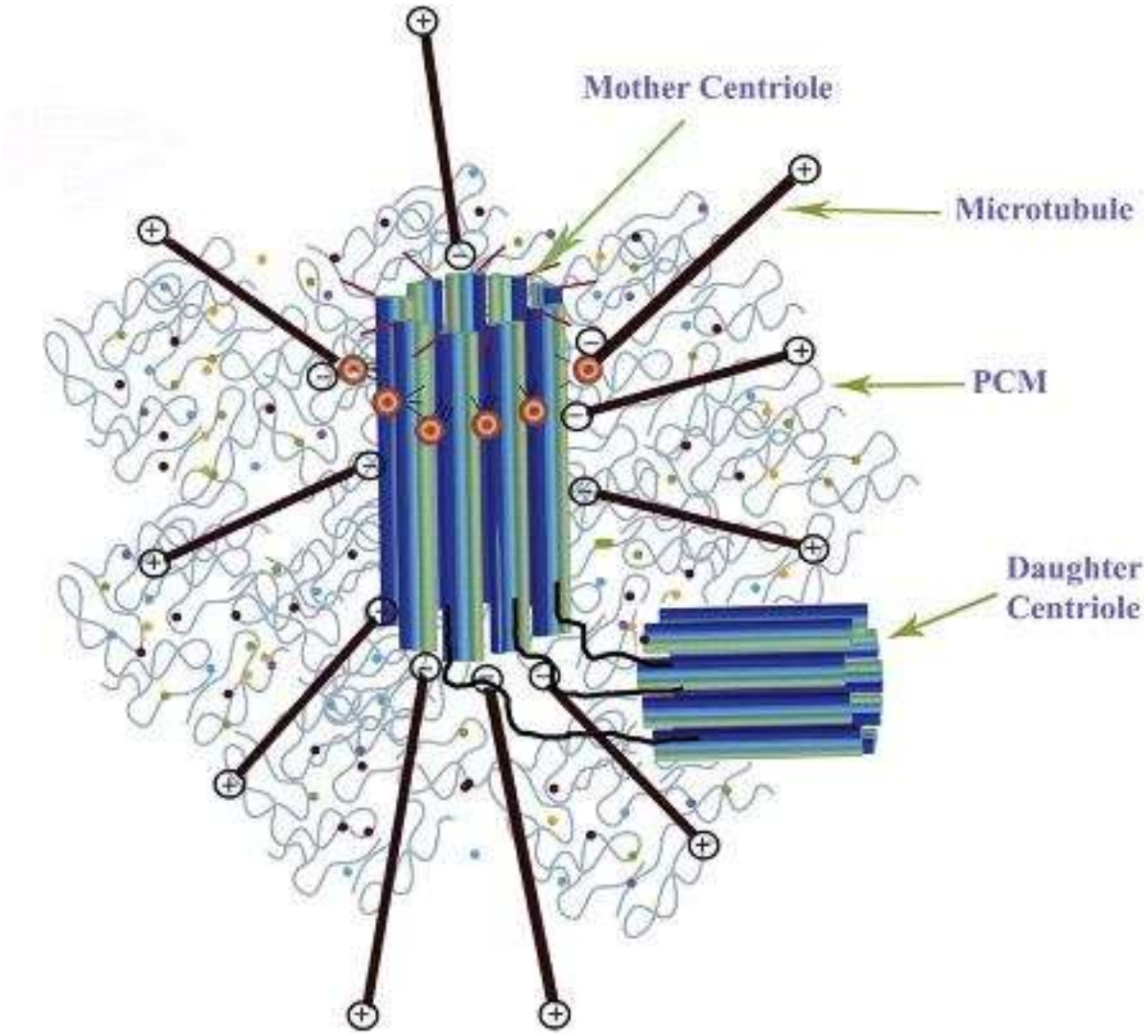
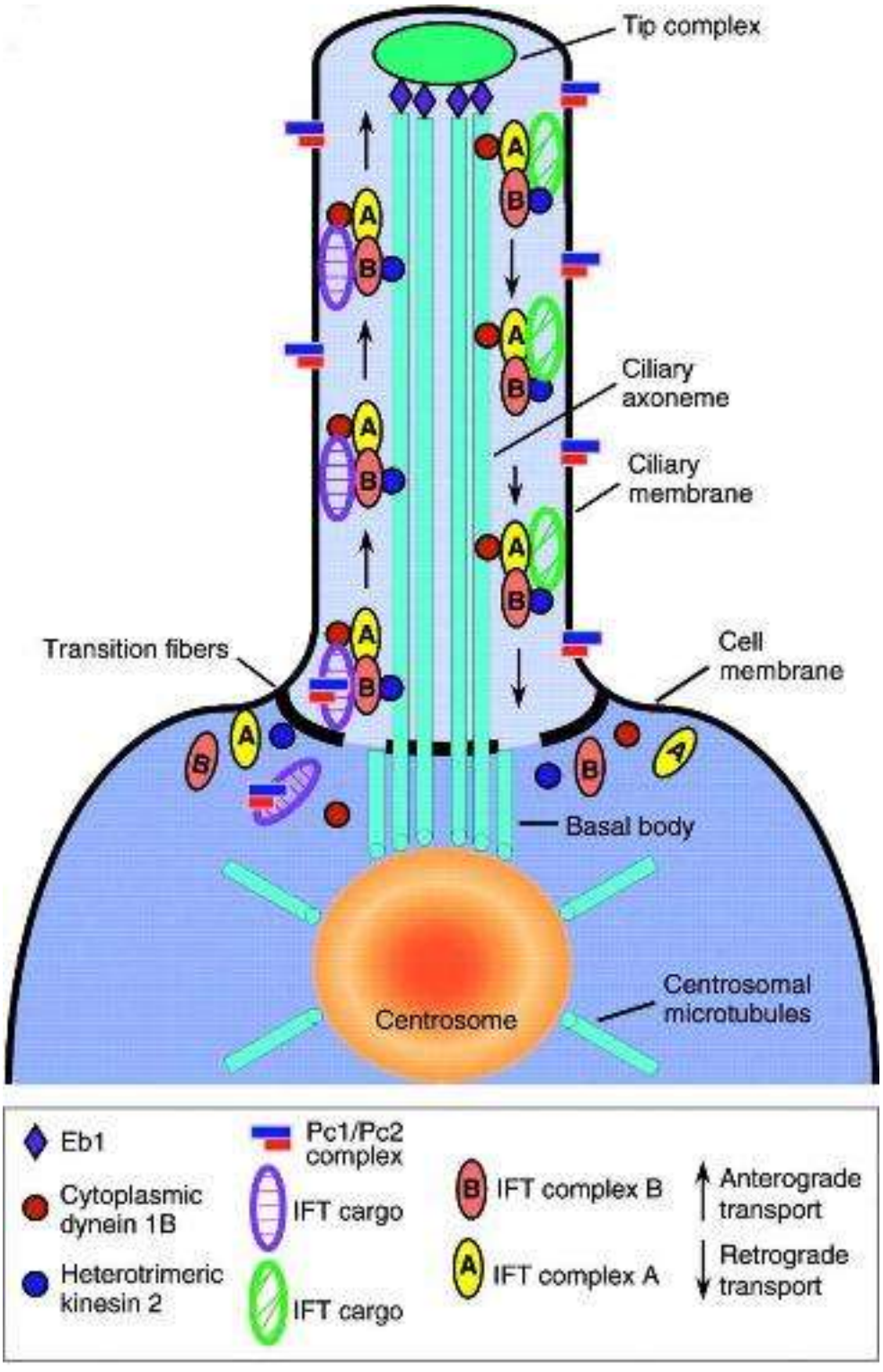


Fig. 27

Centrioles are embedded in centrosomal material consisting of a scaffolding lattice with a large amount of coiled-coil centrosome proteins (Pericentriolar Material PCM). Its 3D architecture is sustained by protein interactions. Cytosol microtubules are anchored with their minus ends to the centrosome. Their growth is regulated by distal plus-end addition of tubulin. Microtubule numbers and lengths are regulated throughout the cell cycle for specific cellular needs, including shape, signal and vesicle transmission and organelle anchoring. Rapid change is vital for nuclear migrations in the fertilized oocyte to unite maternal and paternal genomes. In mammals (except for rodents), the sperm contributes the centriole to the fertilized oocyte that duplicates during the pronuclear stage and separates after syngamy to act as mitotic centers during all subsequent cell divisions. Adapted from: *The role of centrosomes in mammalian fertilization and its significance for ICSI, by H. Shatten, Qing-Yean Sun.*

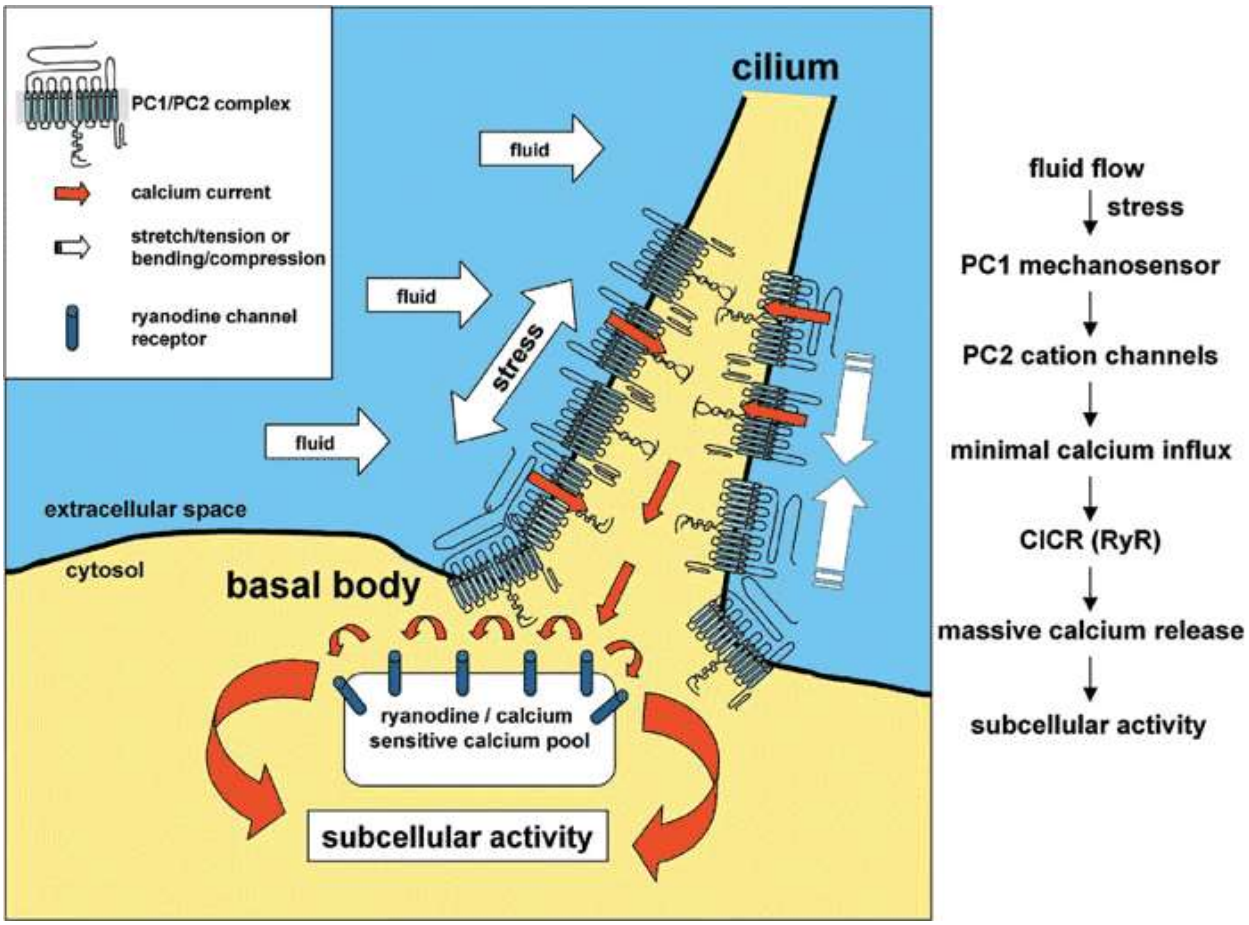
Primary Cilia Dynamics:


Tip complex
Ciliary axoneme
Ciliary membrane
Transition fibers
Cell membrane
Basal body
Centrosome
Centrosomal microtubules
A
B
Eb1
Cytoplasmic dynein 1B
Heterotrimeric kinesin 2
Pc1/Pc2 complex
IFT cargo
IFT cargo
IFT complex B
IFT complex A
Anterograde transport
Retrograde transport

The primary cilium acts as a sensory organelle that transfers information from the extracellular environment to the cell interior. For example, cation channels composed of the proteins Pc1and Pc2 in the ciliary membrane can act as calcium ion channels and sense mechanical stress, while receptors such as the platelet-derived growth factor receptor (Pdgfr) and various others sense extracellular ligands. The processing and transfer of signaling information to the cell is mediated by many specialized proteins, including smoothened (Smo), and microtubule-associated protein complexes that include members of the nephronophthisis protein family [Nphp, inversin (Invs)], and proteins associated with Bardet-Biedl syndrome (BBS). Signals from primary cilia ultimately are involved in regulating crucial cellular processes, including the cell cycle, cytoskeletal organization, intraflagellar transport and signaling pathways, such as the hedgehog, canonical and non-canonical Wnt/planar cell polarity (PCP) pathways and others. Abbreviations: Apc2, anaphase promoting complex protein 2; Dvl1, dishevelled; Nek8, NIMA-related kinase 8; Ofd1, oral-facial-digital type 1 protein; Pcm1, pericentriolar material protein 1. Note that ion channels and signal receptors can be transported into and out of the primary ciium as cargo by intraflagellar transport (IFT) complexes which are moved along microtubules by the motor molecules kinesin and dynein.

Fig. 28

Primary Cilium as a Mechanical Receptor:



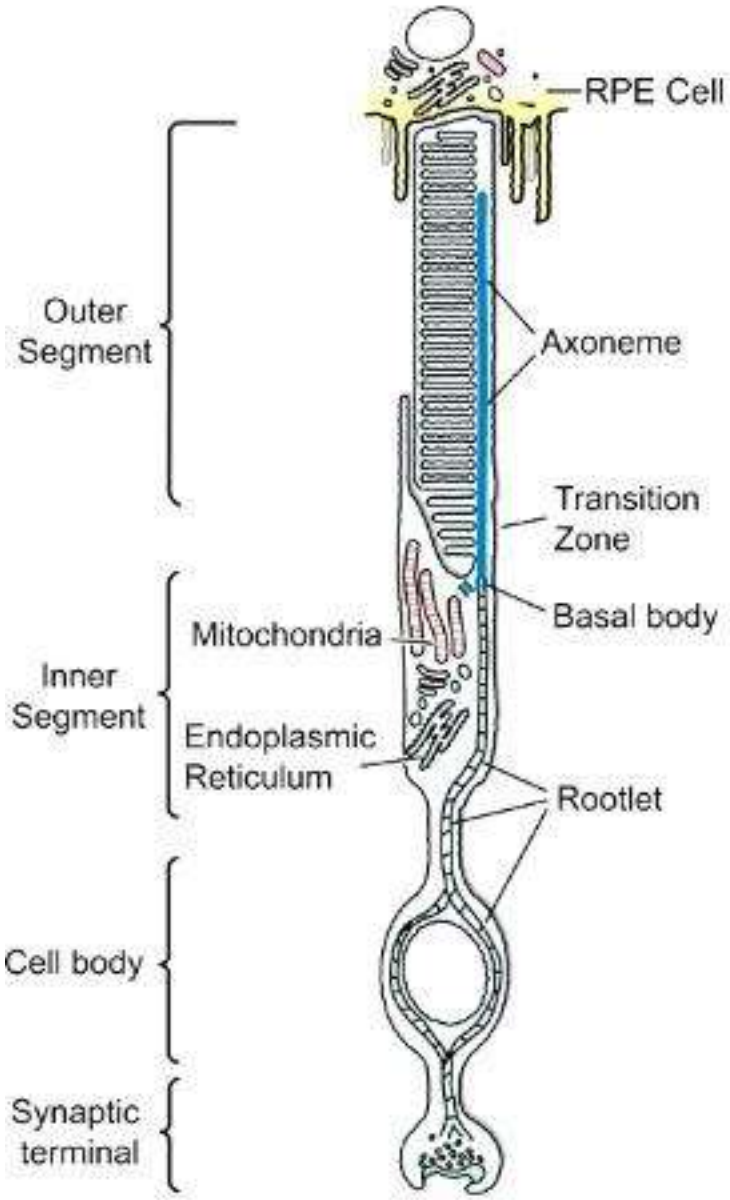
The neo cortex or new brain has expanded with evolution of the higher mammals. The large expansion with humans has enfolded the limb or edge around the top of the brain stem. The Cingulate cortex, the Hippocampus and the Hippocampal gyrus constitute the Limbic cortex. These cortical areas are associated with the ancient brains of the lower mammals and reptiles. Together with some related structures in the diagram and the Hypothalamus this constitutes the Limbic System. It does not include the corpus callosum or most of the thalamus. The new brain to which we owe our intellectual capacity has no direct biological control over our ancient Limbic brain associated with our visceral emotions. We depend on the three dimensions of System 4 to find an appropriate balance between them in the way we make value judgements. How the six Particular Terms of System 4 provide polar insight into the three dimensions is illustrated below.

Fig. 29

The large extracellular channel domain of PC1 is sensitive to fluid flow which internally activates PC2 channels to allow enough Ca2+ influx to activate intracellular ryanodine receptors (RyR) that result in a large calcium induced release of Ca2+ ions (CIRC). The increase in cytosolic calcium ions regulates many molecular events inside the cell that contribute to tissue development. This is one of many Ca2+ related processes in cells of various organs in this case important in kidneys. Calcium signalling regulates the regenerative mode of System 4.

Cilia in Rod and Cone Cells of the Retina:

Rod Photoreceptor Cell



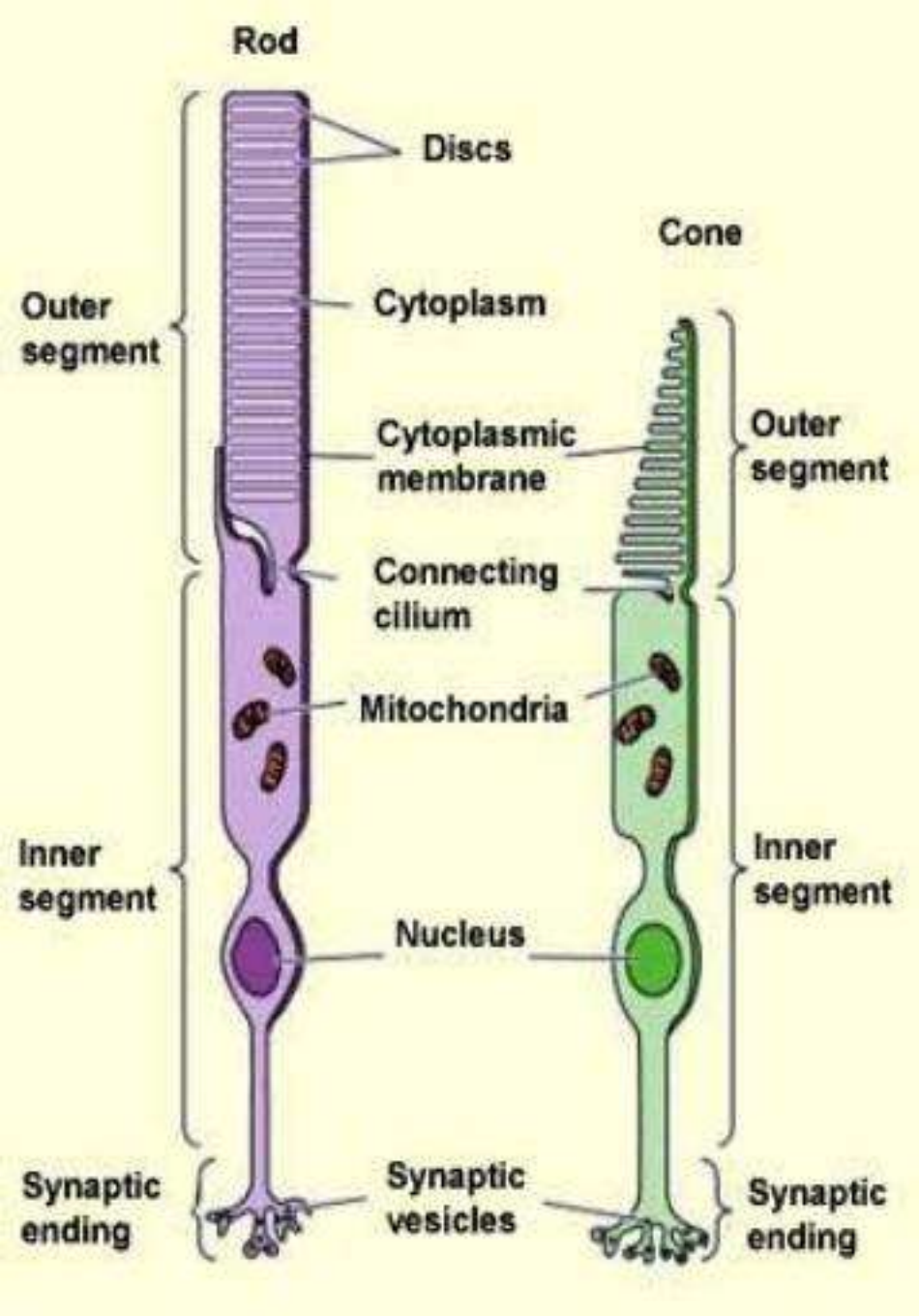


Fig. 30

The stacked structures of rod and cone outer segments that repond to light are elaborate extensions of the primary cilia axoneme of each cell. The complex grows from the centriole that forms the basal body. The axoneme is an antenna system receiving electromagnetic input in the visible spectrum. The signal is transmitted via four synapses to the visual cortex where higher Systems generate virtual images. This 4 Step visual pathway is consistent with System 4 Term transforms from Term 4 that receives the sensory input at rods and cones through T2 and T8, to the T5 Production of input to the higher Systems of the visual cortex. T1 concerns each cell's capacity and T7 the storage of memory in all cells involved in the pathway. The System 4 transform sequences can be traced synapse by synapse. Other senses also use cilia and work in analogous ways.

Complementary Signaling Patterns:

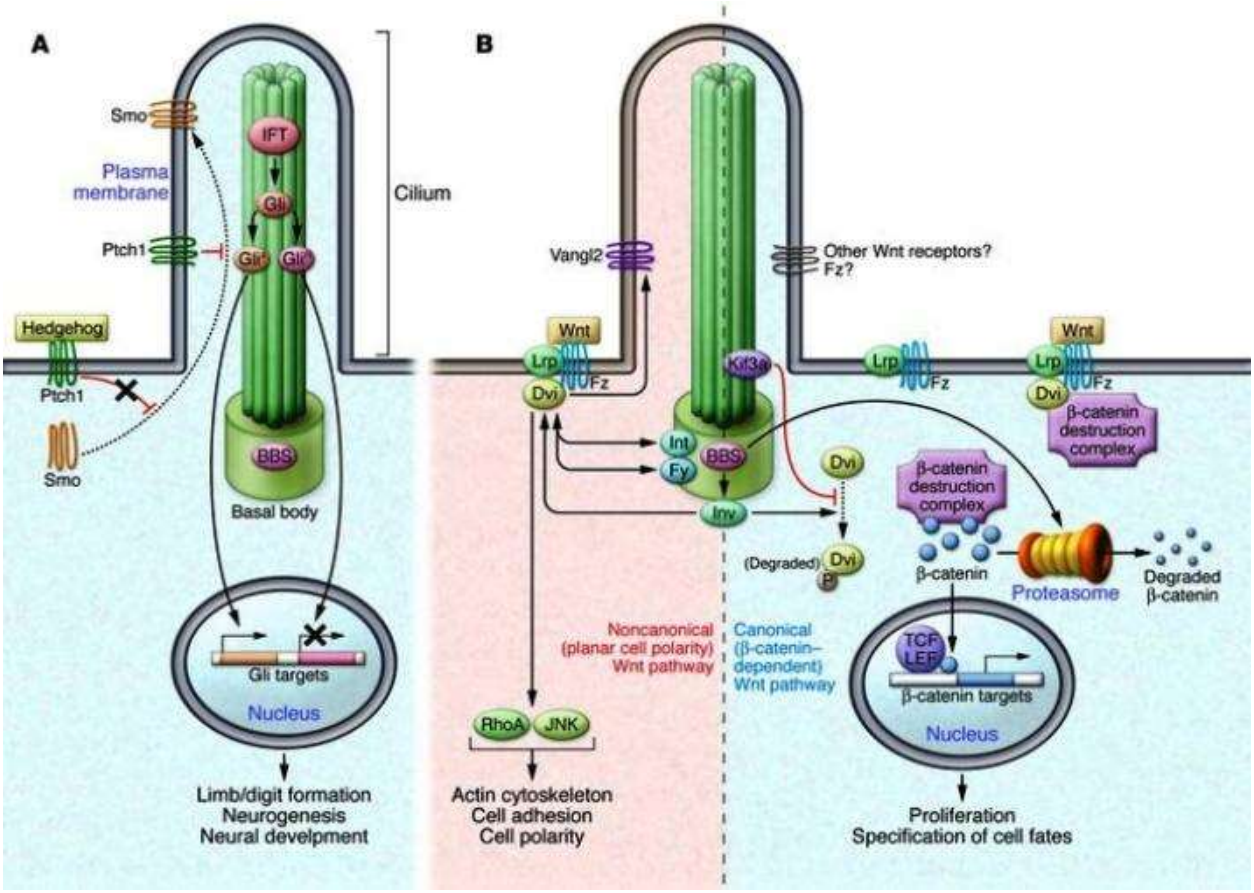


Fig. 31

Membrane receptors and channels can be cycled in and out of the primary cilium by the intraflagelar transport (IFT) complex illustrated in Figure 28. This can select, adjust, activate or inactivate signaling pathways critical for development, adaptation, and maintenance gene expression according to the physiological context between Cells, Organs and Host. IFT can adjust trafficking at various rates according to the balance required (Pan and Snell 2005). Growth factor, morphogen, odorant, and hormone receptors, ion channels, and multipass G-protein - coupled receptors have all been shown to localize to the ciliary membrane. (Marchall and Nonaka 2006)). Although the full complement of primary cilia receptors and channels is not yet known, targeted analyses have already yielded a remarkable diversity.

Growth factor receptors are coupled to mitogenic signaling cascades (MAPKs) and ion channels. In addition to Platelet Derived Growth Factor receptors (PDGFR-aa), stimulation of cilium localized Epidermal Growth Factor Receptor (EGFR) leads to calcium influx via the polycyctin calcium channel (Ma et al., 2005). The downstream signaling cascades are of a regenerative nature. Also, Fibroblast Growth Factor (FGF) has been shown to modulate cilium length (Neugebauer et al., 2009). The complete repertoire of cilium related growth factors is still not known.

Unlike membrane processes in the rest of the cell, signaling molecules or second messengers leaving the cilium are localized at the basal body and centrosome which is positioned to regulate traffic to the nucleus and other destinations in the cell.

Morphogens such as those of the Wnt and Hedgehog (Hh) families influence cell fate and tissue architecture in the developing fetus of the Host through the agency of the pimary cilia. In conjunction with other factors these signaling families exhibit mutual polar restraint (antagonists) suggestive of expressive and regenerative modes hierarchically subsumed by the overall development of the fetus. It is clear that primary cilia play central roles in signaling related to cell fate differentiation, development, maintenance and the coherent integration of Cell function with Organs and the Host human being.

Hierarchical Relationship between Host, Organs and Cells:

We host human beings have evolved over several billion years up the ladder of sentient awareness and we are indebted to our evolutionary history. We are dependent on our plant and animal ancestors for our physical survival. Through our global endeavors we have assumed responsibility for their descendants that still share the planet with us. With the evolution of the vertebrate quadruped limb structure came the parallel development of an autonomic nervous system distinct from a somatic nervous system.

The autonomic nervous system fuels the patterned emotional energy needed for cerebral thought and somatic action. As the Host of our physical bodies we employ our nervous system to regulate our thoughts, feelings and actions. Many of our human autonomic patterns of emotional feeling have evolved from behavioral patterns worked out by our quadruped vertebrate ancestors and subsequently tailored by social requirements that have accompanied the development of language.

Autonomic emotional patterns are reflected into cerebral awareness by the Limbic system that constitutes an emotional brain. We are not at liberty to function soley on blind emotion even though we remain anchored to our natural heritage. The right and left hemispheres of the neo cortex or new brain became functionally distinct from one another with the development of language and both sides lack the emotional coloring of the primitive limbic brain. They nevertheless seek a meaningful balance with the emotional patterns projected into cerebral awareness by the limbic brain.

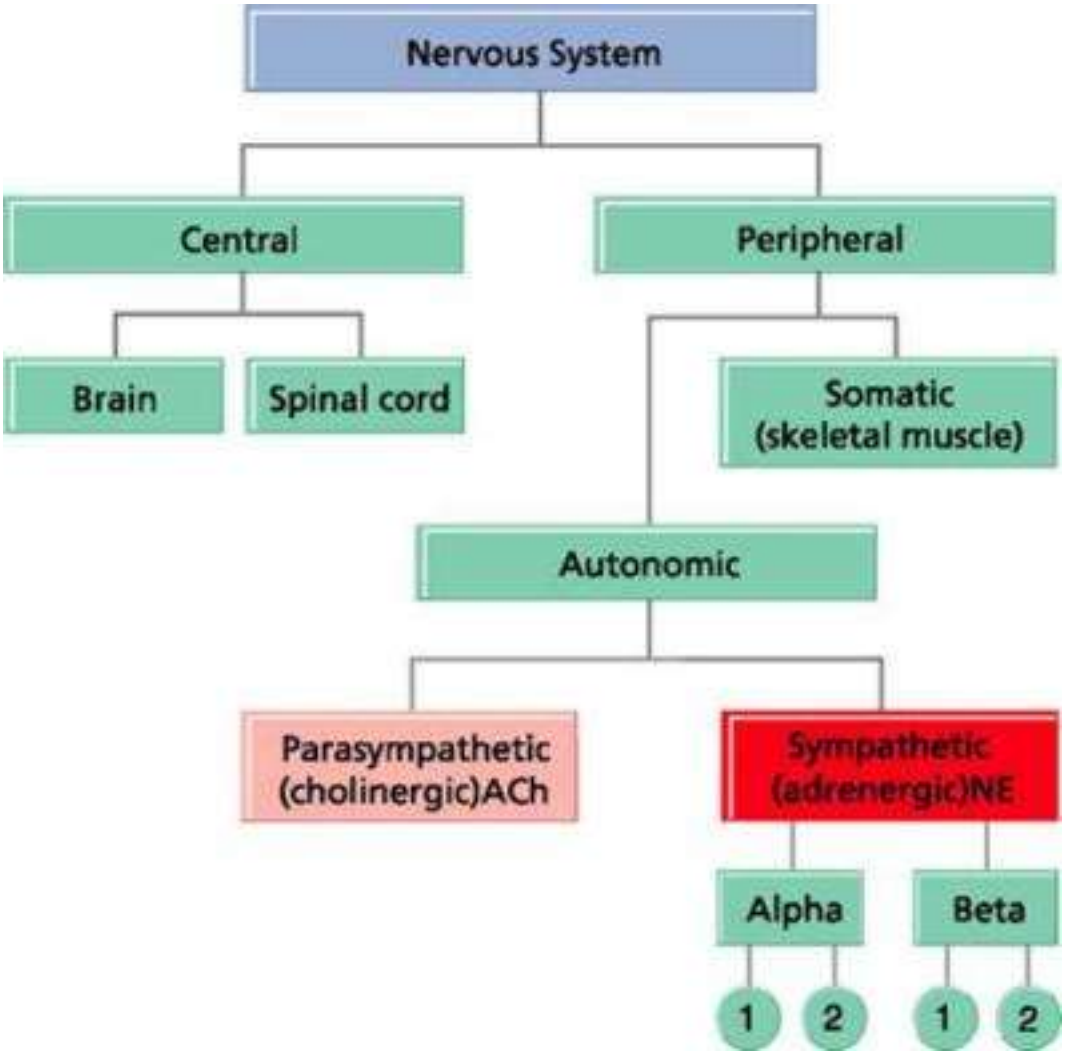
The linguistic left hemisphere deals in linear logic and reason in our socially evolved context. It develops and implements techniques of behavior accordingly, from mastering housekeeping and cooking to learning horsemanship or tennis, to performing duties in a daily job. Likewise the practice of science and mathematics is a left brain language endeavor concerned with techniques of verbal and mathematical language that constitute disciplined objective thought.

In contrast the mute intuitive right brain is holistic and concerned with timeless integrating themes as opposed to left brain causal determinism, syllogism, algorithm and systems of logic. The right brain excels at aesthetics of design rather than techniques of execution. It appreciates how things fit together as a whole. It has a spiritual concern with qualities as distinct from quantities. The right hemisphere is the building architect and design engineer. The left hemisphere transforms the design into a quantified physical result. Each hemisphere also subsumes self similar characteristics within it due to the way the System elaborates within itself. In addition to the right and left primary sensory and motor areas of the neocortex each hemisphere also has secondary sensory and motor areas.

We function in social, spiritual and natural environments. Our left brain functions in a social environment that is transient and changing moment to moment. Our right brain functions in an eternal spiritual environment. It seeks out timeless themes that never change yet determine the patterns of all change. Likewise science seeks out universal laws that prescribe change but never change. Our right brain quest seeks out the cosmic order whether through genuine religious or scientific pursuits. Both are subject to rigid involutionary dogma in practice of course.

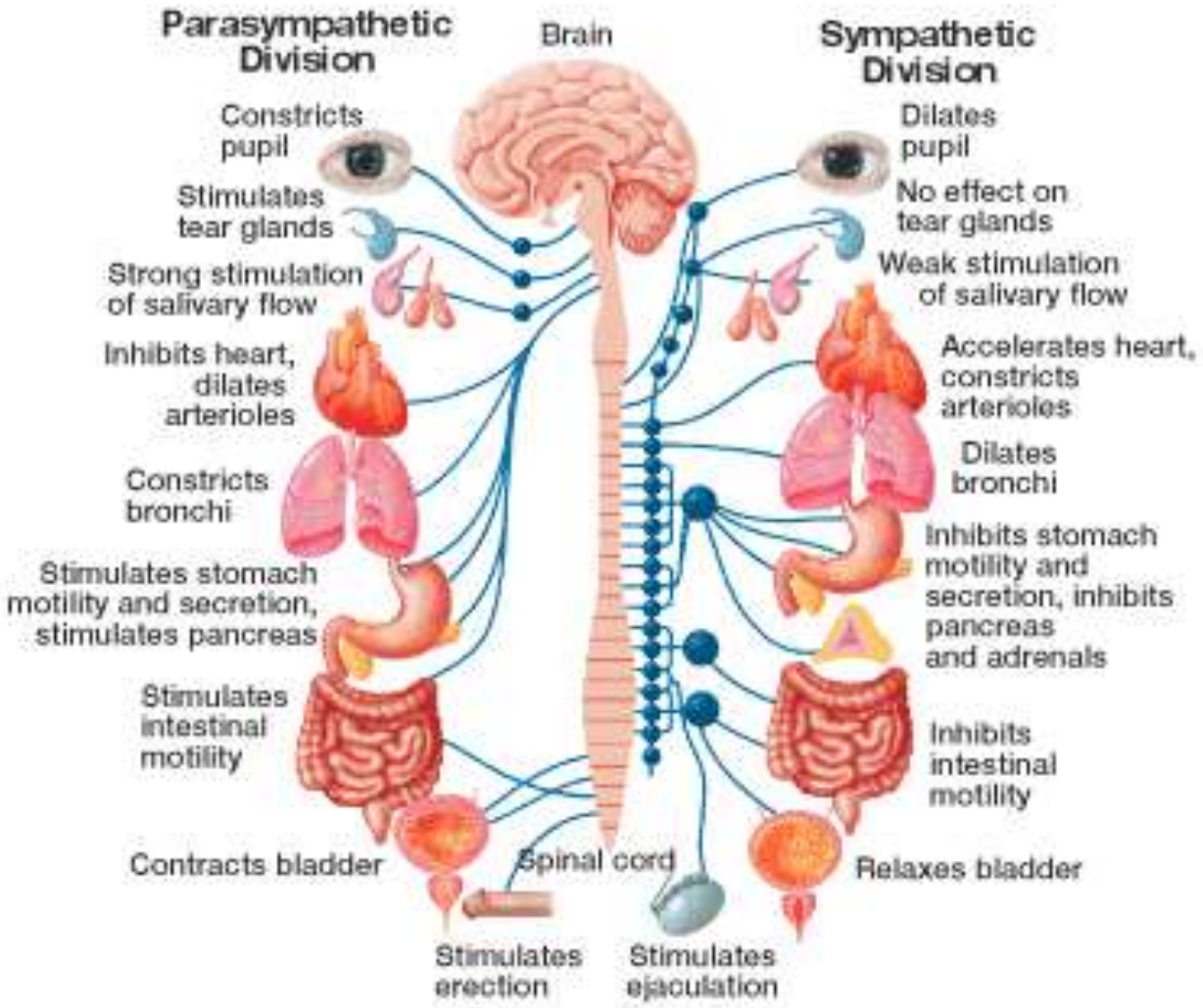
We have however evolved up through the tiers of evolution according to how the cosmic order works. This requires that our left and right brains find a meaningful balance with our ancient limbic brain that fuels them. This imposes appropriate tailoring of our limbic brain emotional impulses in determining our social responses according to intuitively perceived qualities implicit in our evolving circumstance.

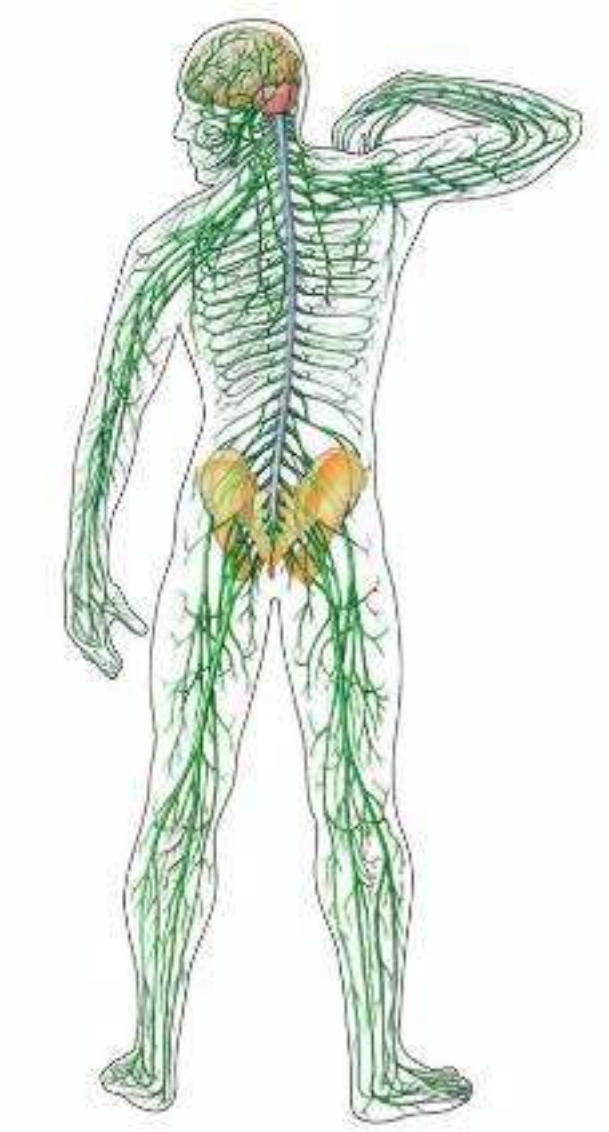
Our nervous system is the primary instrument that we employ to mobilize all of our other various organs according to our resources of intuitive insight, acquired knowledge and emotional energy. Our value judgments that determine behavior result from the related three polar dimensions of System 4. The many trillions of cells of our body respond to the extent that they are able.


Nervous System
Central
Peripheral
Brain
Spinal cord
Somatic
(skeletal muscle)
Autonomic
Parasympathetic
(cholinergic)ACh
Sympathetic
(adrenergic)NE
Alpha
Beta
1
2
1
2

The central nervous system (CNS) consists of the head brain and the spinal cord. Primary somatic sensory nerves have their cell bodies outside the CNS and transmit via a four neuron pathway to response elements such as muscles that exhibit action potentials like neurons that animate the skeletal structure of the body. As pointed out in the Figure 30 note a self-similar 4 neuron pathway projects from sensory input to cortical areas of the cerebrum. This is consistent with four of the six Term transforms of System 4, namely Terms 4, 2, 8 and 5. Term 1 relates to membrane readiness. Term 7 memory is keyed to protein synthesis in each pathway cell. The autonomic nervous system is structured in an analogous fashion. The sympathetic and parasympathetic nervous systems work in mutual polar restraint with the exception of the genital functions. Erection is a parasympathetic function. Ejaculation is a sympathetic function. The sympathetic alpha and beta receptors facilitate activation or restraint.

Fig. 32

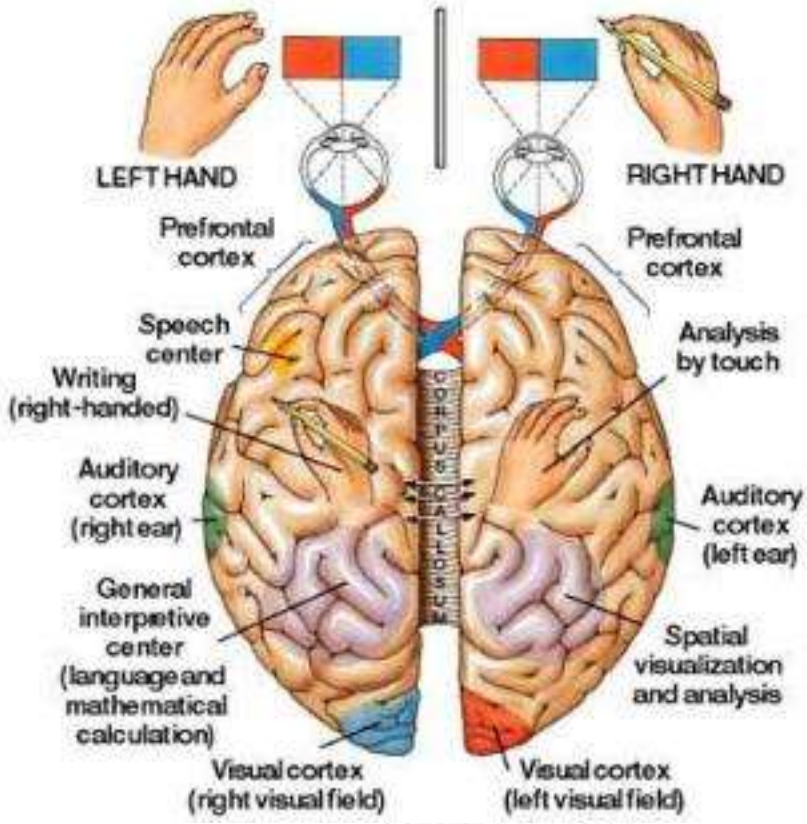

Parasympathetic Division
Brain
Sympathetic Division
Constricts pupil
Dilates pupil
Stimulates tear glands
No effect on tear glands
Strong stimulation of salivary flow
Weak stimulation of salivary flow
Inhibits heart, dilates arterioles
Accelerates heart, constricts arterioles
Constricts bronchi
Dilates bronchi
Stimulates stomach motility and secretion, stimulates pancreas
Inhibits stomach motility and secretion, inhibits pancreas and adrenals
Stimulates intestinal motility
Inhibits intestinal motility
Contracts bladder
Spinal cord
Relaxes bladder
Stimulates erection
Stimulates ejaculation

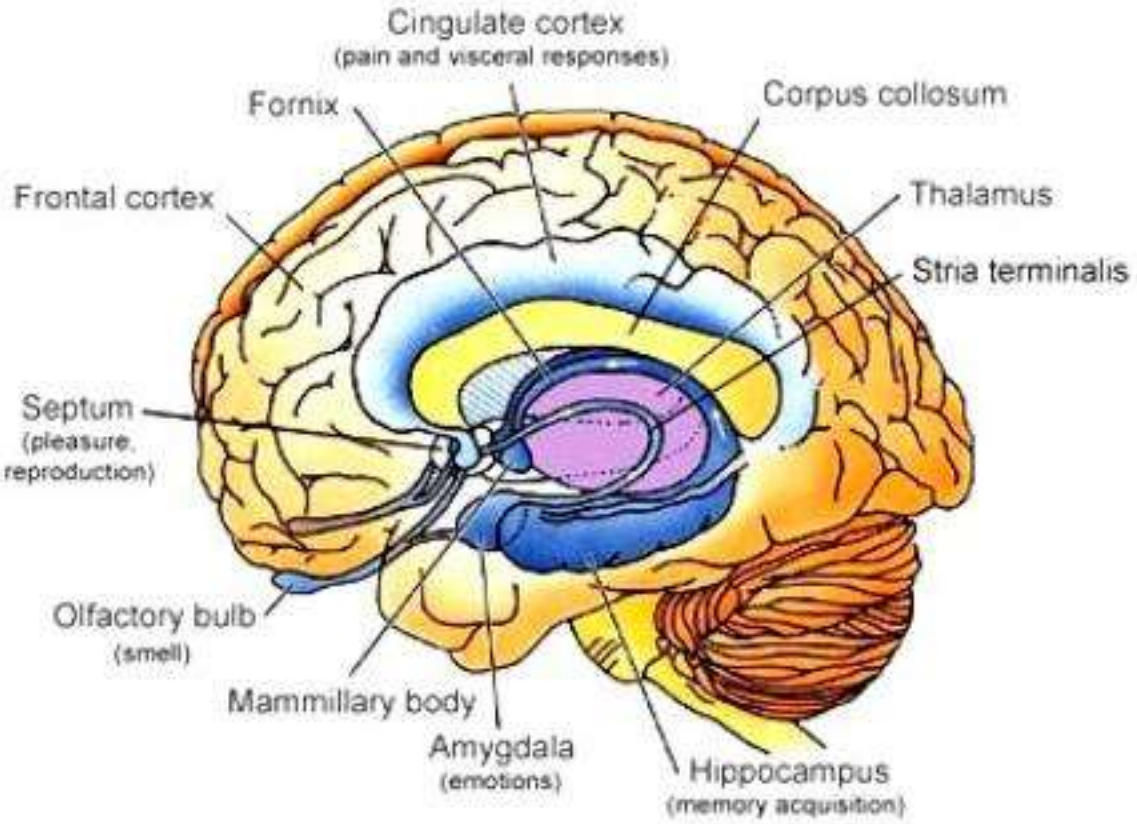


Autonomic Nervous System

Fig. 33
Somatic Nervous System

Fig. 34


LEFT HAND
RIGHT HAND
Prefrontal cortex
Prefrontal cortex
Speech center
Writing (right-handed)
Analysis by touch
Auditory cortex (right ear)
Auditory cortex (left ear)
General interpretive center (language and mathematical calculation)
Spatial visualization and analysis
Visual cortex (right visual field)
Visual cortex (left visual field)


Cingulate cortex
(pain and visceral responses)
Fornix
Corpus collosum
Frontal cortex
Thalamus
Stria terminalis
Septum
(pleasure, reproduction)
Olfactory bulb
(smell)
Mammillary body
Amygdala
(emotions)
Hippocampus
(memory acquisition)

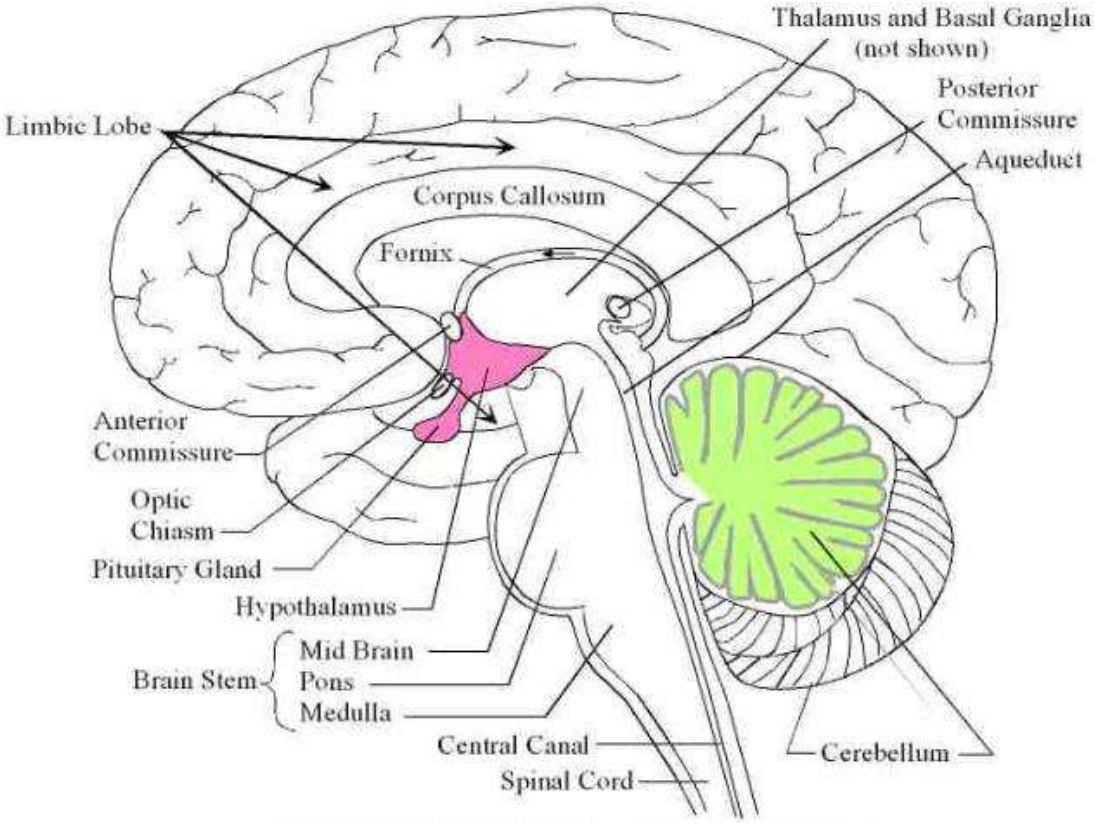
Hemispheres of the Neo-Cortex

Fig. 35

Limbic System

Fig. 36

Fig. 37

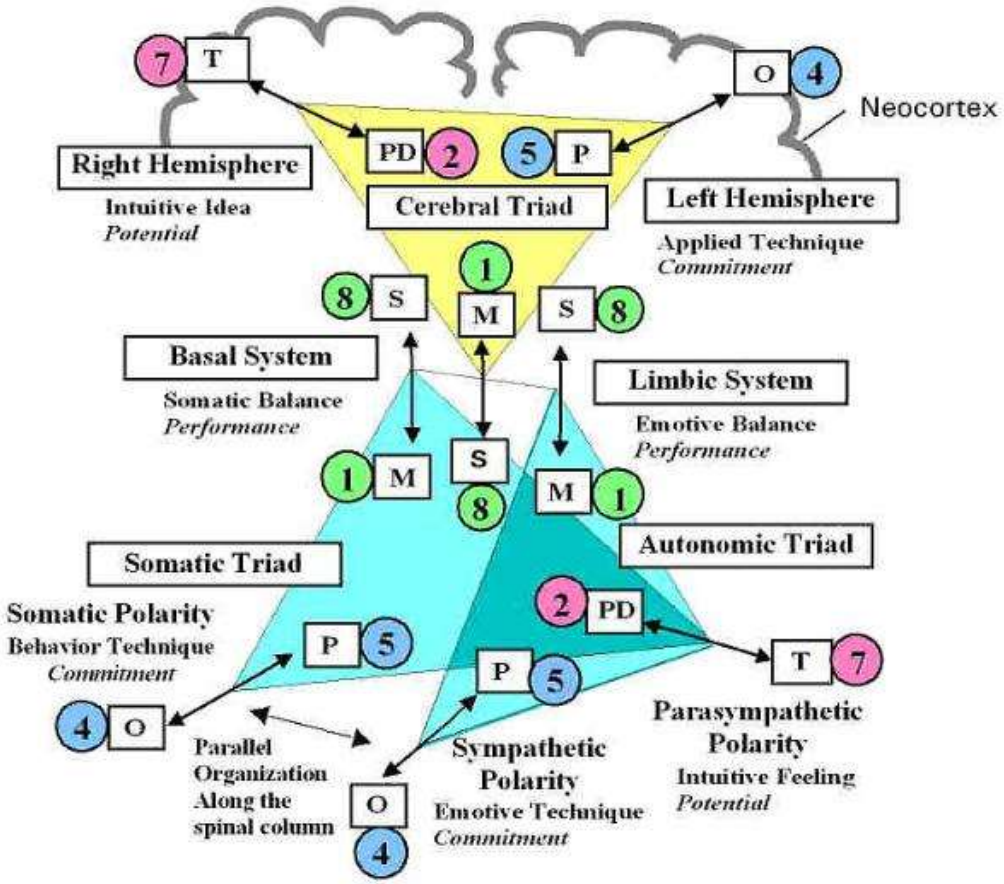


THE HYPOTHALAMUS and CEREBELLUM

The hypothalamus receives major inputs from the limbic system via several routes, including the fornix. It projects back to the limbic cortex, thus maintaining intimate two way communication with it. The hypothalamus integrates visceral sensory information from the body's internal organs. Descending projections from the hypothalamus are relayed via two reticulospinal tracts, one activating autonomic functions, the other influencing somatic activity. Direct connection to the pituitary gland complements autonomic innervation of the endocrine system. The hypothalamus is thus centrally concerned with the feedback of emotional input to the process of conscious thought. It likewise fuels the body's somatic muscular activity via the autonomic nervous system.

The cerebellum is shown sectioned through the vermis, together with the brain stem. The cerebellum receives dense projections from the motor and sensory areas of the neocortex, relayed through the pons. It also receives widespread input from other areas of the central nervous system, limbic system and brain stem, including all sensory systems. It receives proprioceptive input about the body's position in space from throughout the body. The cerebellum projects to the vestibular system concerned with balance and also to the motor system. Some motor projections go to the primary motor area of the neocortex, via the thalamus. Others go to the red nucleus in the brain stem which in turn projects both to the primary motor cortex and to the motor horns of the spinal cord. Other motor projections go to both descending reticulospinal tracts. The two descending tracts of the reticular system, one somatic, and one autonomic, are multisynaptic and thus allow for the integration of activity at different spinal levels. The cerebellum is thus situated to effect a balance between the three polar dimensions of nervous system activity. A somatic balance determines behavior parallel to a balance between conscious thought and emotion.

(Adapted from Science and Cosmic Order)



COMPANY & NERVOUS SYSTEM INTEGRATION

The same symbols can be used to illustrate the integration of a business organization and the integration of the human nervous system. They are both expressions of the creative process, a business organization being an extension of how we ourselves integrate experience. Thus the right brain PD ⟷T polarity focuses on Product Development (PD) within the context of the Treasury (T). The treasury is the resource capacity necessary to make the idea a reality. In a company the treasury mirrors the facilities, resources and creative potential, while in a human it is a treasury of memory, both physical and mental capacities, that determine the person's creative potential. Practical ideas must relate to the resources essential to translate them into form. Left brain technique then Produces the ideas in behavioural form in relation to our social Organization, as in the P ⟷ O polarity. In a company the Production effort works in the context of the Organization structure. The third S⟷M polarity relates Sales to the Market. In a human it balances one's emotional and physical performance to appropriateness in the social and natural environment. The Basal System that parallels the Limbic System concerns the somatic balance of ideation and behavior, which complements the emotive balance. The Basal System is made up of the basal ganglia, most of the thalamus, the cerebellum, and much of the brain stem. Note that the Autonomic and Somatic triads are the Market for cerebral mentation and vice versa. The limbic and basal polarities thus mediate tentative balances between thought, feeling and behavior, to the extent that there is accurate insight into ***potential, commitment*** and ***performance.*** Learning from experience takes place on this basis, often through trial and error. System 4 Term numbers are shown in color cicles.

Fig 38

System 4 Particular Term Sequence:

System 4 has a Universal Hierarchy that elaborates on and is consistent with Systems 1, 2 and 3 that transcend and subsume it. The hierarchy is specified by the Primary Universal Term, Term 9. It applies to all biological processes including cells, organs, host human beings, as well as our socio-economic organizations and corporations. It applies as well to fetal development and evolutionary history. Gene expression is a cell function that responds to the needs of the human host.

In each host Cell, ***Idea*** is implicit in the integrating electronic pattern of ion and electron exchange. ***Knowledge*** is implicit in the cell infrastructure including organelles, membranes, cytoskeleton, transport mechanisms and the like. ***Routine*** is regulated by teams of enzymes that catalyze coherent sequences of pathway events. ***Form*** is given by molecular synthesis for expressive export (eg. cells of the endocrine glands) as well as for regenerative cell development and maintenance. These four active interfaces are also called Centers designated "C".

The Universal Hierarchy is ***Idea C1*** → ***Knowledge C2***→ ***Routine C3***→ ***Form C4***.

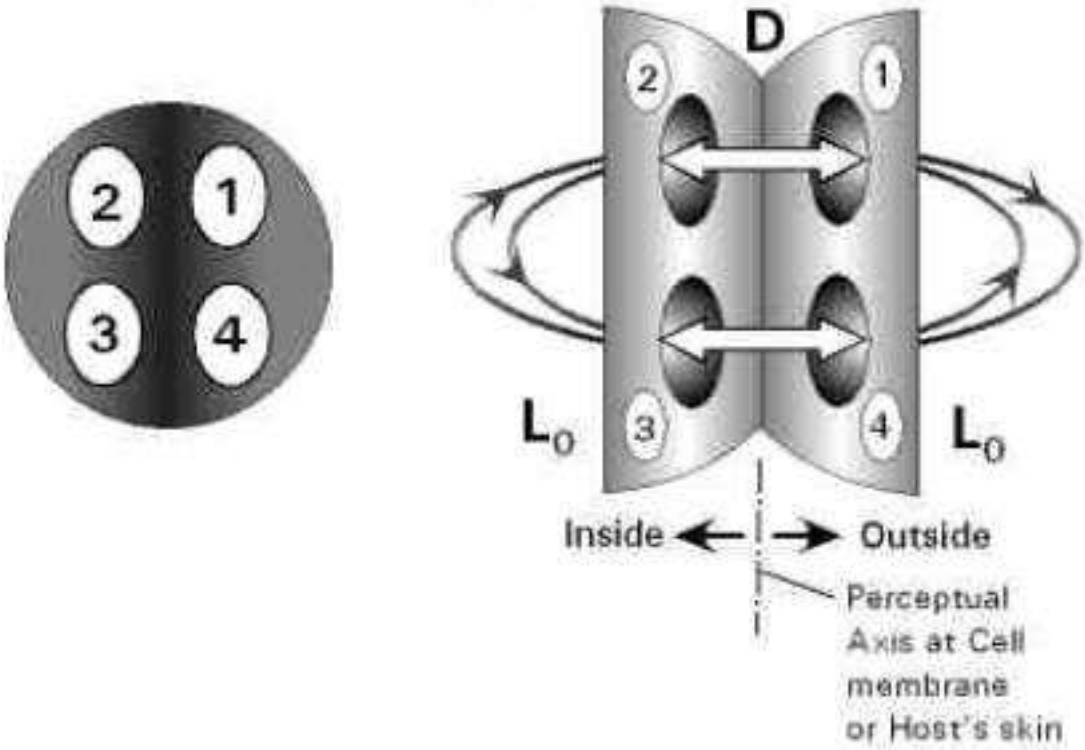
Center 1: Electronic Pattern (Overall integrating ***Idea*** pattern in various Cell Types of Organ Tissues)
Center 2: Organelles (Vested ***Knowledge*** such as Membranes, Chromatin, Ribosomes, Primary Cilia, etc.)
Center 3: Enzyme Teams (Enzymes catalyze chemical ***Routines*** that commit energy resources to pathway streams)
Center 4: Molecular Forms (Covalent Chemical Reactions ***Form*** the cell and its export products)

In the Human Host the overall hierarchy is electronic ***Ideas*** in the brain direct the ***Knowledge*** implicit in how our Organs such as nerves and muscles are structured to mutually interrelate. This in turn coherently directs the ***Routines*** of specific groups of Cells such as motor neurons and muscles to alter the physical ***Form*** of the Body with respect to the environment. Every activity of the human host is intimately linked to all organs and cells of the body from simply breathing to running a race.

The sequence of System 4 Particular Term transformations illustrated in Figure 39 below show how the six Step transform sequence applies to a cell. There are self-similar homologues to how it applies to a human host and to a business corporation. The Centers in each Term relate from a common active inside or center (designated light **L0**) to a common passive outside (designated darkness **D**). The Universal Term sequences that regulate the Particular Term sequence are not shown. They deserve a separate article. The small colored boxes in each Particular Term diagram in Figure 39 relate to human and corporate behavior respectively.

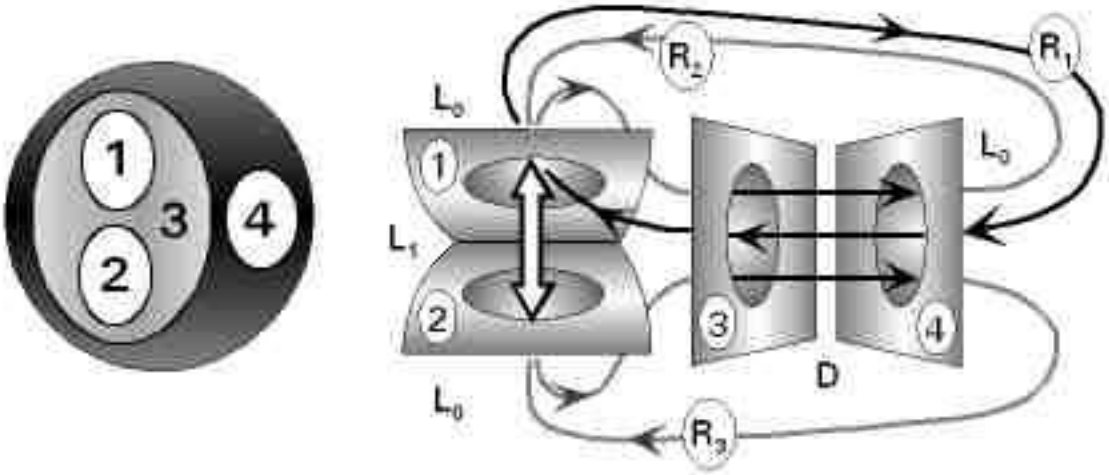
Host cells and the host human being work in self-similar ways that are interrelated by the orthogonal centrioles and Primary Cilia consistent with Systems 4 and 5 respectively. Their nine sets of microtubule structures communicate by channeling the energy transformations involved. As pointed out previously System 5 works as two reciprocating System 4s one relating to the external environment and one relating to the internal environment. The energy transformations in each case are channeled by the mother and daughter centriole respectively. This relates the internal processes of the Cell to Organs and to the Host human being.

Term 1E: Response Readiness



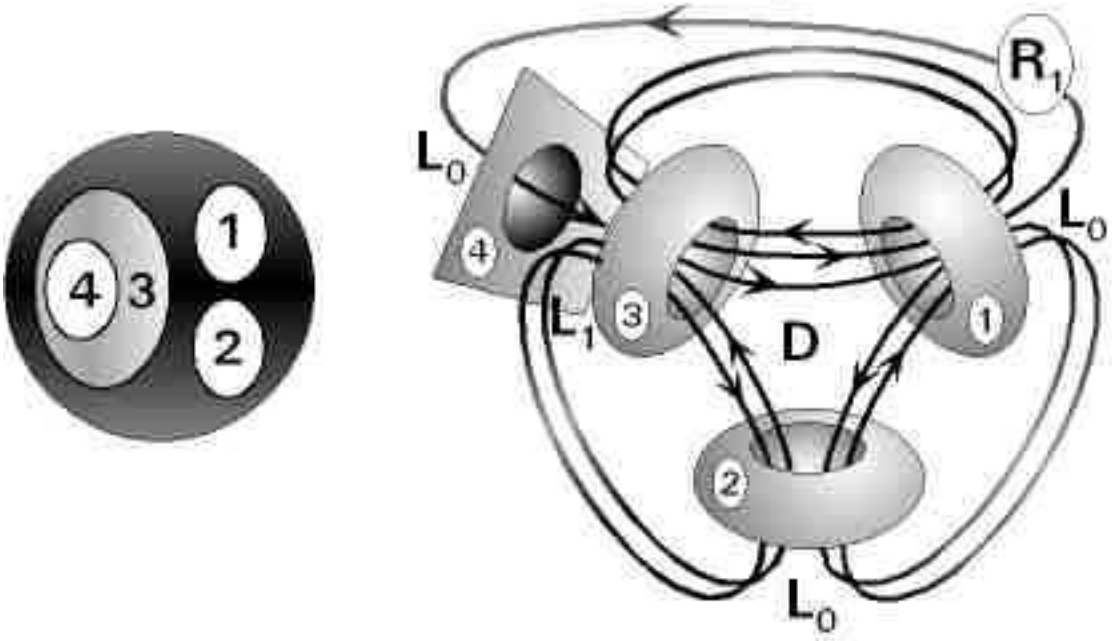
T1E: Inside the Cell, Organelles Center 2 (**C2**) such as membranes, cytoskeleton, vesicles, ribosomes, metabolons etc. are aligned inside with Enzyme Teams **C3** that catalyze Routines. Organelles **C2** are coalesced with Electronic Patterns **C1** outside the cell such as membrane potentials and signal receptors that represent the readiness of the cell to respond. **C1** is aligned outside the cell with the molecular Form **C4** of the cell. **C4** is coalesced with Enzyme Teams **C3** inside the cell. This primes the readiness of **C3** enzymes that regulate chemical signalling cascades and protein synthesis that result in the molecular Forms **C4** of the cell and its export products. TheT1E term thus reflects the state of readiness and the capacity of each cell type to respond. When **C1** and **C2** change places Ca2+ ions **C1** are sequestered inside with respect to organelles **C2.** This allows ready regulation of the regenerative mode T1R. T1 is a Marketing function that reflects the capacity of the cell to respond to sensed needs. It is also the human perception of the capacity to respond to felt needs. T1 transforms to T4 preserving the **C1=C2** coalescence.

Term 4E: Sensory Organization



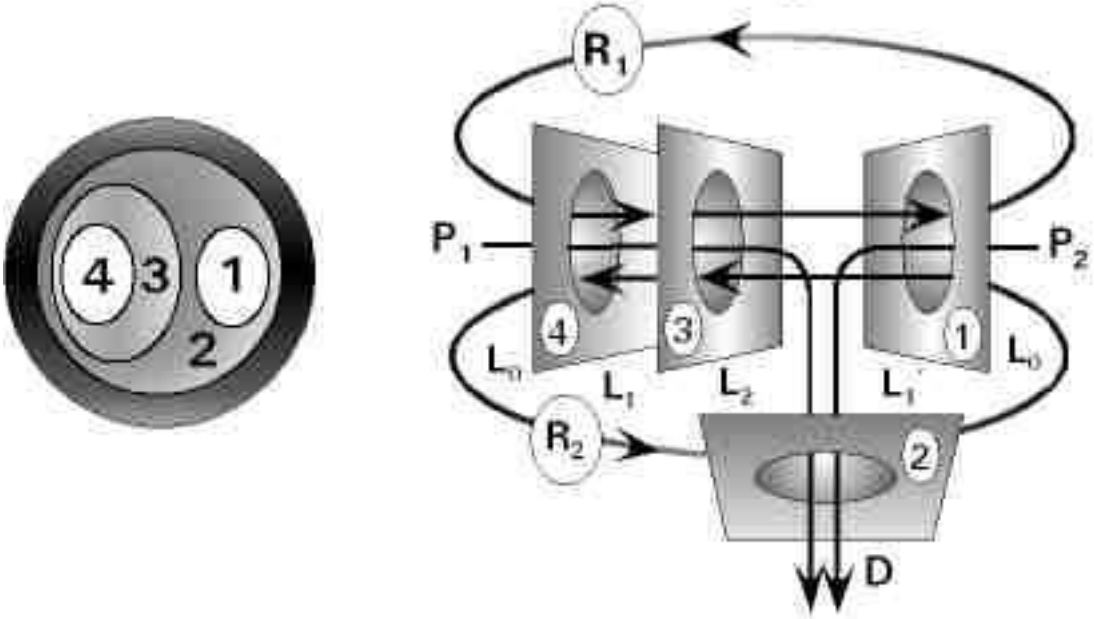
T4E: Electronic patterns **C1** are coalesced with organelles **C2** and direct enzyme teams **C3** as a coalesced group to catalyze all patterned Molecular Forms **C4** in the whole cell (**R2** and **R3** illustrate this). A specific signalling cascade **R1** initiated from outside the cell relates molecular Forms **C4** to electronic patterns **C1** through relevant enzyme teams **C3**. **R1** docks with an electronic interface **C1** coalesced with an organelle **C2**, such as a chromatin gene transcription sequence at a gene promoter site. When **C1** and **C2** change places in the regenerative mode **R1** docks on Ca2+ ion channel receptors of an organelle **C2** such as at the Endoplasmic Reticulum (ER). **C2** is coalesced with the electronic pattern **C1** of the organelle that works in concert with the relevant enzyme teams **C3** that catalyze the appropriate Molecular Formation **C4**. This first messenger **R1** signal can initiate the second messenger release of sequestered Ca2+ ions in the T2R next Step to regulate regenerative cell maintenance. T4 specifies the sensory organization of the cell. In a corporation it is the organized human resources that respond in patterned ways to outside input from customers and regulatory authorities. In a human it is organized sensory input. T4 transforms to T2 when **C3** turns inward to face **C1** and **C2** and links with them to form a triad.

Term 2E: Product or Idea Development



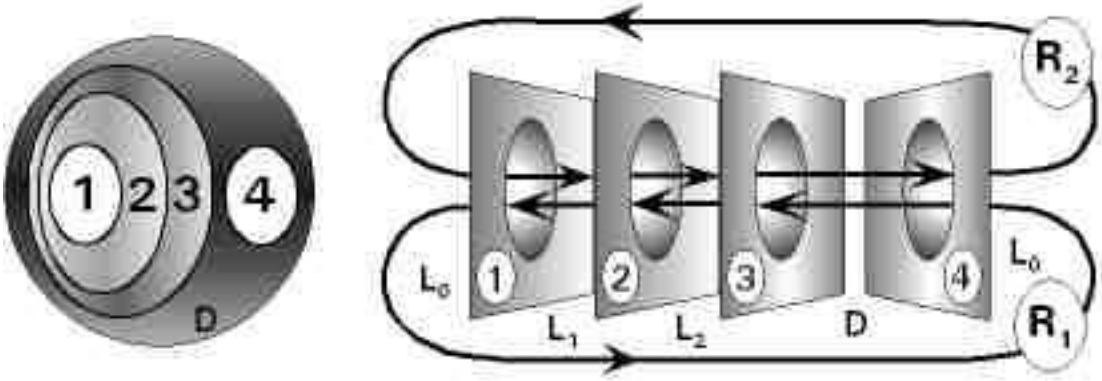
T2E: C1, **C2** and **C3** are mutually distinct yet intimately linked as a triad. The same **R1** signal from T4E is now superimposed on this intimate triad. The molecular form **C4** of the **R1** signal directs Enzyme Teams **C3** to catalyze specific electronic patterns **C1** in intimate association with organelles **C2** such as an organized group of transcription factors at and near a promoter site for a gene. This designs and organizes an integrated mRNA transcription pattern at gene promoter sites assembled from a complement of factors and ncRNAs. This includes prescribing a short signal sequence to mRNA that addresses it to ER ribosomes for expressive mode export from the cell. In T2R **C1** and **C2** change places. **R1** is now directed to organelles **C2** with second messenger Ca2+ ion release from sequestered stores that prescribe regenerative transcription patterns at genes in concert with electronic patterns C1 in the triad. Ca2+ ion transport also facilitates neural activity and readies muscle action for human Host behavior. T2 is an Engineering Design function that transforms to T8E which is a Sales function relating to the quantity of transcription Designed and Engineered by T2E for production export.

Term 8E: Motor or Transcription Response



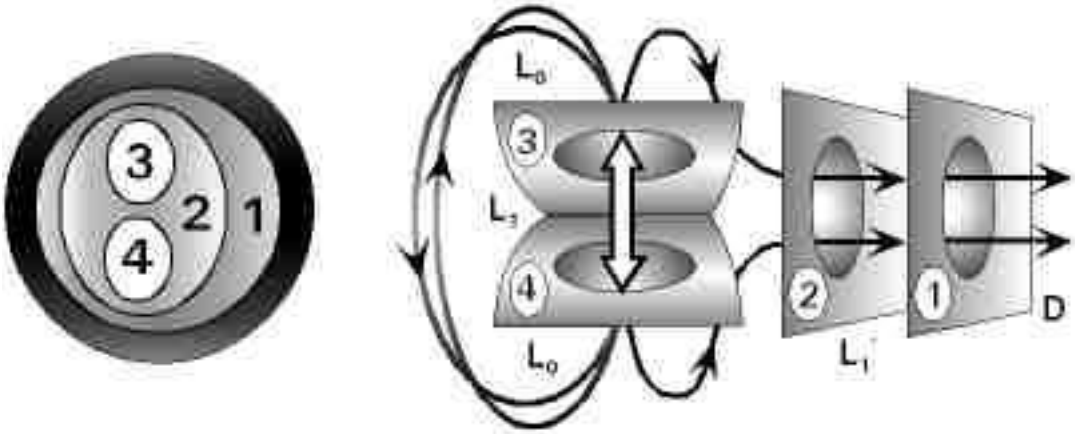
T8E: The same **R1** now operates within organelles **C2**. It invites a countercurrent **R2** that is a balanced electronic response **C1** via Enzyme Teams **C3** that activates and regulates Molecular Forms **C4** such as gene transcription factors, enhancers, silencers and ncRNAs to balance demand **R1** with supply **R2** according to available energy resources. **P1** represents energy supply (glucose) from molecular input **C4** via enzymes **C3** to organelles **C2**, such as mitochondria to make ATP. **P1** balances **P2** which represents energy expenditure of electronic processes involved in transcription **R2.** In the cell the many transcription factors, cofactors and ncRNAs cooperate to balance demand **P2** with available energy supply **P1** as distributed by the Universal T8R Term. The particular Term T8E is always in the expressive mode. The regenerative mode is the Primary Universal Term T8R that distributes total available energy from food to all body cells according to a priority of needs. In the human Host **R2** represents a specific pattern of motor neuron projections to muscles. T8E is a Sales Term in corporate parlance. It transforms to the T5 Production Term.

Term 5E: Physical Act or Protein Production



T5E: R2 from T8E employs RNA transcribed from genes in T8E to assemble covalent electronic bonds **C1** of amino acids at ER ribosome organelles **C2** via enzymes **C3** to produce & process protein molecules **C4** for export from the cell. A new **R1** in T5E represents Molecular feedback in which **C4** transports enzymes **C3** in vesicles from the Golgi back to the ER for recycling use in a later **R2** sequence. In T5R **C1** and **C2** change places. Membrane ion transport channels **C2** release Ca2+ ion **C1** concentrations from stores, such as from the ER, Golgi, and mitochondria. The second messenger Ca2+ ions **C1** in turn direct enzyme teams **C3** in regenerative molecular processes **C4** such as protein synthesis in the cytosol rather than at the ER. Ca2+ ion release also plays a role at neuron synapses for body responses. T5 is the Production Department that produces human behavior also. T5 transforms to T7.

Term 7E: Memory or Energy Pattern Resource



C3=C4 Enzyme Teams are coalesced with Molecular Formation. This element of catalyzed technique is the core of memory within the organelles **C2** involved in the whole pathway sequence, such as membranes, nuclear chromatin, nucleolus, the ER, Golgi, vesicles, transport channels, microtubule mechanisms etc. Together this accounts for the expenditure of electronic energy in the cell **C1** for each pathway. This balancing of accounts is facilitated by **P1** and **P2** of both the Particular T8E Term for the cell and the Universal T8R Term for the whole body. When **C1** and **C2** change places T7R budgets for the electronic needs **C1** of organelles **C2** in a regenerative pathway for cell maintenance needs consistent with the distribution of energy resources for the whole body by the universal T8R Term. The core element of technique **C3=C4** relates to each specific pathway. T7 transforms to T1 in successive Cycles with the **C1=C2** coalescence in T7 aligned with the **C3=C4** coalescence in T1. The recall process from T7 is tensionally coupled to T4 sensory signaling input because the **C1=C2** coalescence of T4 complements the **C3=C4** core of memory coalescence in T7. In this way recall of a specific technique is always relevant to current sensory input in the ongoing flux of circumstance.

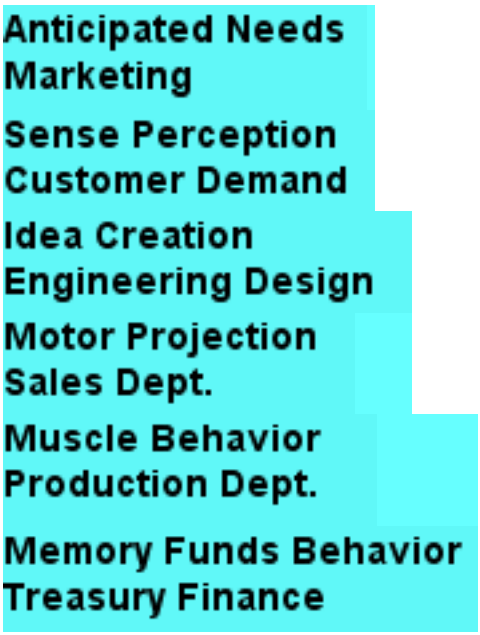
Summary:

The preceding review of gene expression and the maze of factors that influence the pattern of human development, maintenance and behavior correspond to the Term transformations of System 4. Other website articles on the human nervous system as well as other articles on the organization of the cell further confirm this. The role of the orthogonal centrioles and the importance of the primary cilia to vital areas of cell signaling add further empirical weight. Cilia are also critical for receiving sensory input via our sense organs from the natural environment as illustrated by the rods and cones of the retina. The Microtubule Organizing Center (MTOC) with pericentriolar material in which the centrioles are immersed generates the microtubule cytoskeleton that regulates organelle positioning and molecular traffic in the cell.

The common structure of the two centrioles throughout the animal kingdom with a circle of nine triplet sets of microtubules is consistent with the three Cycles of System 4 Term transformations. The two perpendicular centrioles with the mother centriole forming the basal body of the primary cilium protruding from the cell surface underlines the importance of this interpretation. It relates outward to the extracellular environment while the daughter centriole relates inward to the intracellular environment. This is consistent with System 5 that operates as two interacting Systems 4, one closed relating to the internal environment and one open relating to the external environment. For example the somatic nervous system relates to the external environment while the autonomic nervous system relates to the internal environment. This is illustrated in a general way by the somatic and autonomic triads in Figure 37. It is significant that both triads share a common parasympathetic polarity which is concerned with conserving the long term interests of the individual and the species. This places certain energy restraints on both the sympathetic and somatic nervous systems.

Fig. 39

Note: I am gratefully indebted to uncountable sources for this work and hope that I will be forgiven by those I have not acknowledged formally. This work is offered freely for its pragmatic value to all who may be able to use it.



Overall Cell Organiation