5.08.2020.

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II, M.Sc. ZOOLOGY

Unit-III. DEVELOPMENTAL BIOLOGY MZ032

GENES AND DEVELOPMENT.

(1) Introduction.

⇒ The survival of each species of virus, bacteria, fungi, plants (or) animals requires that its individual members multiply to produce new individuals to replace the one killed by the natural death in old age (or) by predators, parasites, environmental pollution (or) other ecological hazards such as shortage of water, oxygen, light, optimum temperature, food etc. The multiplication of a species is

⇒ In asexual reproduction, the progeny arises from a single existing organism which splits buds (or) fragments to give rise to two (or) more offsprings, all of which have hereditary traits identical to those of the parental organisms.

⇒ In sexual reproduction, the progeny arises from the fusion of two genetically distinct gametes (Sperms and eggs of multicellular animals).

⇒ Two different aspects of Ontogenetic development and phylogenetic development

⇒ The ontogenetic development of a species thus includes embryogenesis, the development of a new individual from the fertilized egg (or) zygote.

⇒ Blastogenesis, the development of a new individual from an asexual reproductive body (ie. bud, body fragment, gemmule etc.).

⇒ The field of biology which deals with the study of those embryogenetic and blastogenetic processes by which organism undergoes progressive and orderly changes in structure and function during their entire life history is called Developmental Biology.

⇒ Embryology deals with all aspects (genetical, biochemical, physiological and morphological) of the entire developmental period of the individual organism.

⇒ The embryogenesis of an animal species includes following stages.

(i) Gametogenesis
(ii) Fertilization
(iii) cleavage
(iv) Gastrulation
(v) Organogenesis

Genes and Development

⇒ Genes play a vital role in controlling all of these processes. Genes contain the information a cell needs to make proteins.

⇒ Different genes contain the information needed to make different proteins.

Why the genes are important:

⇒ A gene is a basic unit of heredity in a living organism. Genes come from our parents. We may inherit our physical traits and the likehood of getting certain diseases and conditions from a parent

Why is the nucleus important.

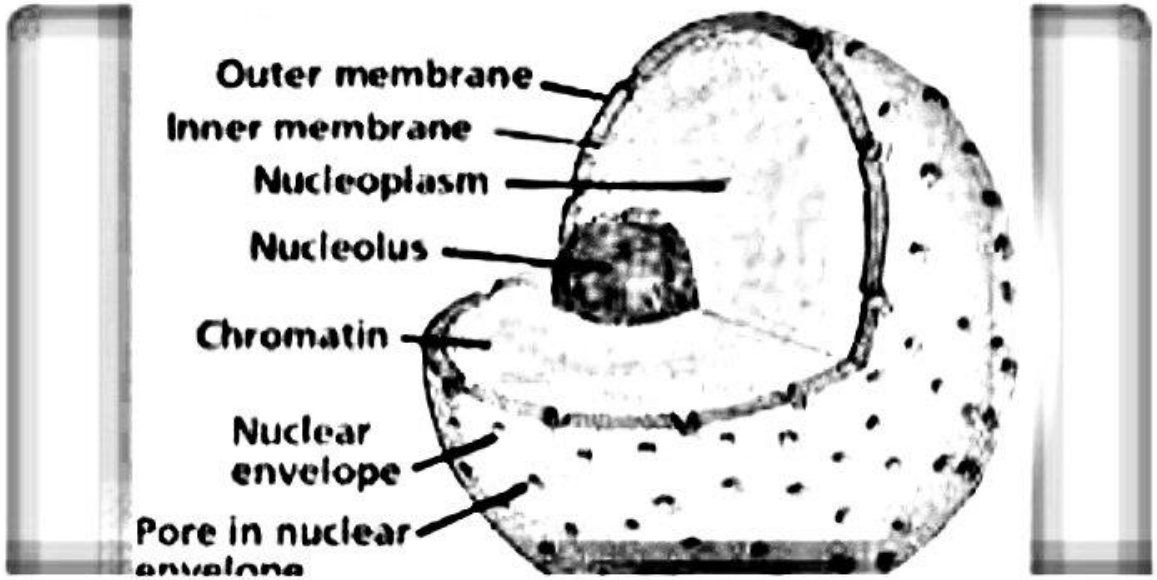
⇒ The nucleus is the most important organelle in the cell.

⇒ It Contains the genetic material, the DNA, which is responsible for Controlling and directing all the activities of the cell.

⇒ All the RNAs needed for the cell are synthesized in the nucleus.

Importance of Nucleus.

⇒ The main function of the cell nucleus is to Control gene expression and mediate the replication of DNA during the cell cycle.



"The **nucleus** is the **most important organelle** in the **cell**. It contains the genetic material, the DNA, which is responsible for controlling and directing all the activities of the **cell**. ... The nucleolus within the **nucleus** is the site for RNA

Nuclear Transplantation

⇒ Nuclear transplantation is a method in which the nucleus of a donor cell is relocated to a target cell that has had its nucleus removed (enucleated)

NUCLEAR TRANSPLANTATIONS:

Transplantation. During experimental work in developmental biology, small pieces may be cut out of embryos in various stages of development and inserted into suitably prepared wounds of the same or another embryo. In the case of transplantation of piece of the same embryo to another place, the transplantation is said to be **autoplastic**. If the transplantation is from one individual to another of the same species, the transplantation is called **homoplastic**. If the transplantation is to an individual of another species belonging to the same genus, the transplantation is **heteroplastic**. A transplantation to an individual more distally related than species of one genus is called **xenoplastic**. The animal (embryo) from which a part is taken is referred to as the **donor** ; the animal to which the part is transplanted is called the **host**.

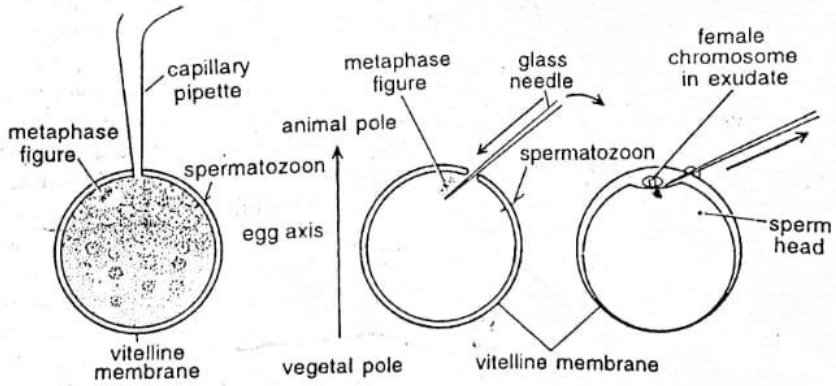
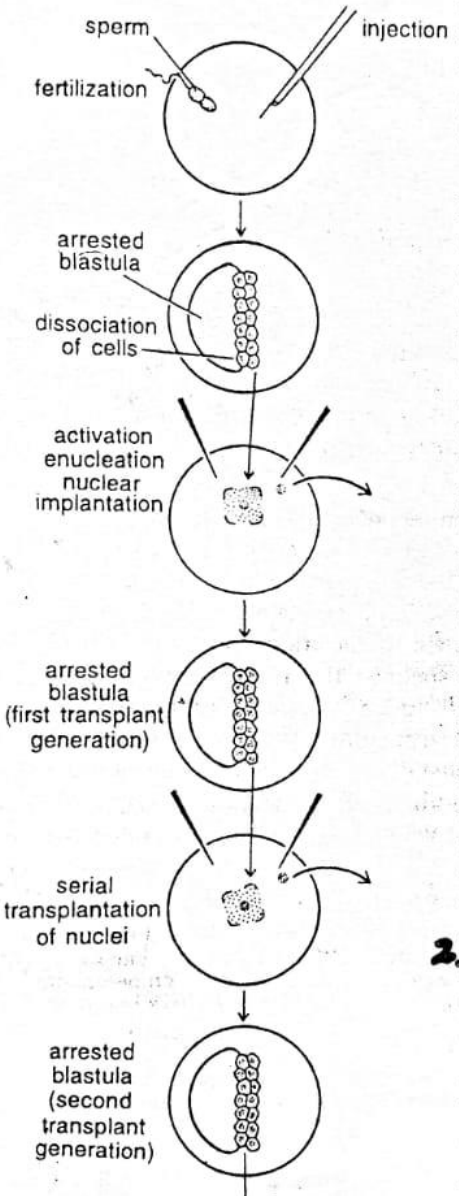


Fig. 1.2. Enucleation of frog egg by means of capillary pipette or glass needle (After Berrill, 1971).

In adult animals, especially highly organized animals such as vertebrates, transplantation is not easy, only autoplastic and homoplastic transplantations usually being successful. In embryos, however, and in lower invertebrates (such as coelenterates), the grafts may heal successfully even after xenoplastic transplantations. Successful transplantations have been carried out between embryos of frogs and salamanders and mammals and birds.

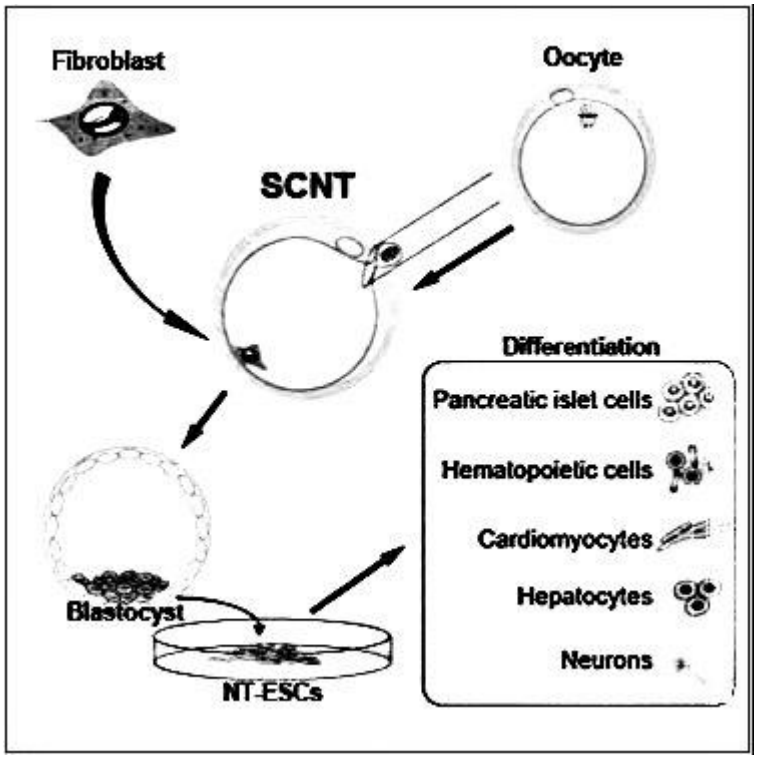


1. Nuclear transplantations. **Briggs** and **King** (1952) have evolved a nuclear transplantation technique for frog eggs and embroys (*Rana pipiens*). The nucleus of an unfertilized egg, which is conveniently located just beneath the animal pole, is effectively removed with a needle or inactivated by ultraviolet light (Fig.1.2). A substitute nucleus is obtained by using a micropipette with a diameter less than that of the particular donor cell, so that the cell is ruptured and the isolated nucleus is obtained. The donor cell may be in the early or late, blastula stage, the gastrula stage, the neurula stage, or even from mature tissues of the functioning tadpole or frog. The last and most difficult step in the procedure involves the insertion of the donor-cell nucleus into the uncleaved enucleated egg. This technique has been extended to

2. serial nuclear transplantation, *i.e.*, donor nuclei, instead of being taken from cells of an embryo developed from a fertilized egg, are taken from an embryo resulting from a nuclear transplantation (Fig.1.3). The nuclei of such cells have an identical set of genes. A further improvement of the

Nuclear transfer
Egg from abattoir ovaries
Mature eggs
Removal of the Shell and genetic material (nucleus) from the cytoplasm
New EMT embryo
Electrofusion
Donor embryo
Separate cells from elite embryo
Recycled
Nuclear transfer embryo
Transferred

Mammary cell donor
Egg cell donor
1
2
Egg cell from ovary
Nucleus removed
Cultured mammary cells
3 Cells fused
Nucleus from mammary cell
4 Grown in culture
Early embryo
5 Implanted in uterus of a third sheep
Surrogate mother
6 Embryonic development
Lamb ("Dolly") genetically identical to mammary cell donor


Fibroblast
Oocyte
SCNT
Differentiation
Pancreatic islet cells
Hematopoietic cells
Cardiomyocytes
Hepatocytes
Neurons
Blastocyst
NT-ESCs

laevis, which contains a single nucleolus instead of the two nucleoli typical of most frogs.

3. Defect. An egg or embryo, after the excision or destruction of a local region, becomes a defect experiment. An egg nucleus can be, thus, destroyed by exposure to X-rays or ultraviolet radiation or sucked out with a micropipette. Cytoplasmic areas can be destroyed by local pricking, heat or ultraviolet treatment. A fine hair can be employed to cut or constrict an egg or cleavage group. Tiny knives, glass needles and scissors are used for excising the parts of embryos. Some regions can be eliminated by their differential susceptibility to toxic substances.

4. Addition. When a part is added to an already completed embryo, as a supernumerary structure, is called **implantation**. By surgical method called **parabiosis**, fusions of whole eggs or early cleavage stages can be accomplished.

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WELCOME TO ALL

II-Msc Zoology

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DEVELOPMENTAL BIOLOGY

UNIT-III

CELLULAR DIFFERENTIATION

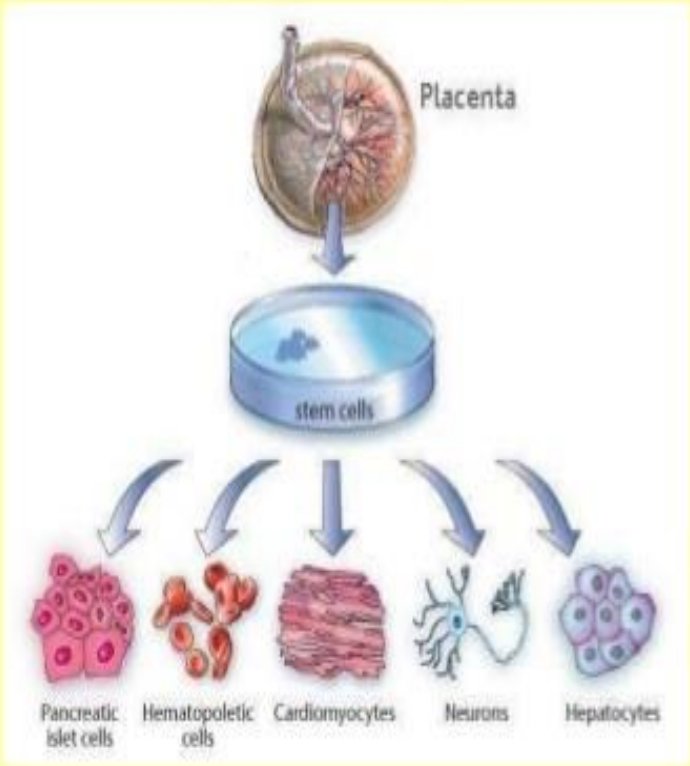
12.08.2020

Cell Differentiation

Specialized Cells

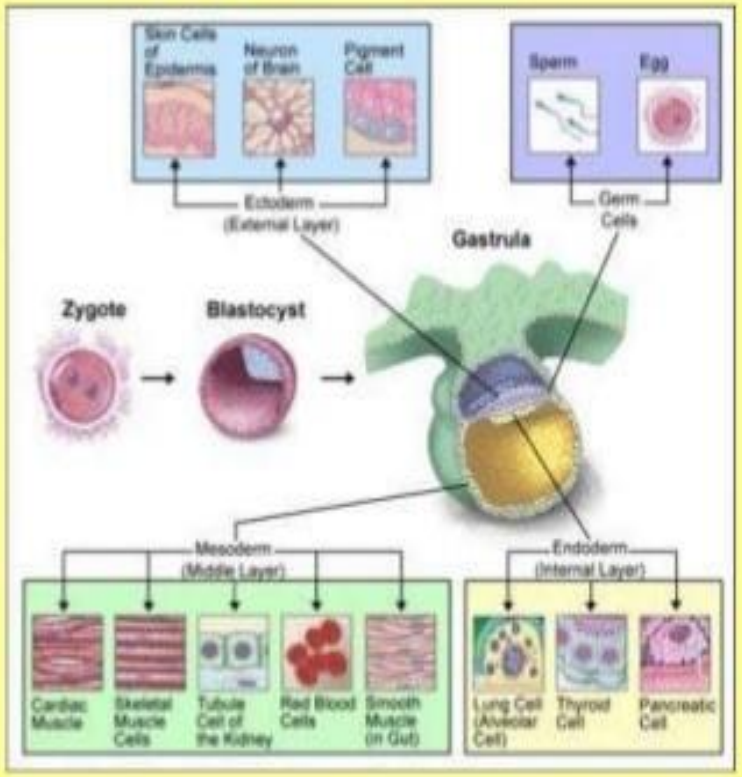
and

Stem Cells



Cell Differentiation

- Multicellular organisms begin as undifferentiated masses of cells
- Variation in DNA expression and gene activity determine the differentiation of cells and ultimately their specialization
- Only specific parts of DNA are activated
- Parts activated determine the function and structure of a cell

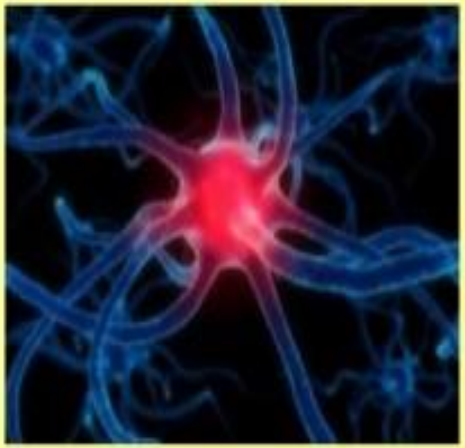


Cell Differentiation

- All cells contain the same DNA so cells initially have the potential to become any type of cell
- Cell Differentiation is irreversible
- All cells in multicellular organism have the same number of chromosomes and DNA

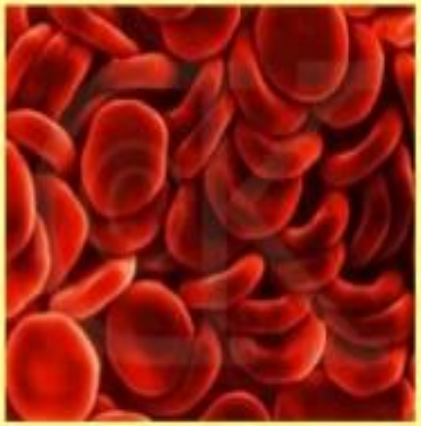
- Different parts of the genetic instructions are used in different types of cells
  - influenced by the cell's environment
- Chemical signals may be released by one cell to influence the development and activity of another cell.

Specialized Cells



Nerve Cells communicate information either by using electric signals (within a cell) or chemical signals (between cells).

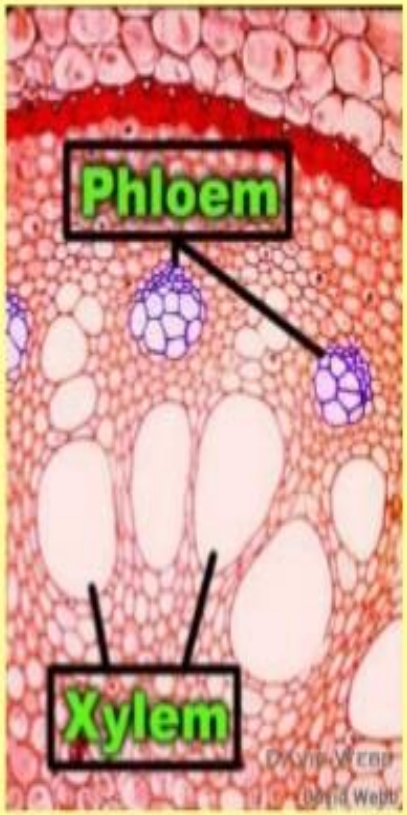
Muscle cells contain protein filaments that slide past one another, producing a contraction that changes both the length and the shape of the cell.



Blood cells are the most common type of blood cell and the vertebrate organism's principal means of delivering oxygen to the body tissues

Specialized Cells

Sperm cells are the male reproductive cell;
the male gamete;

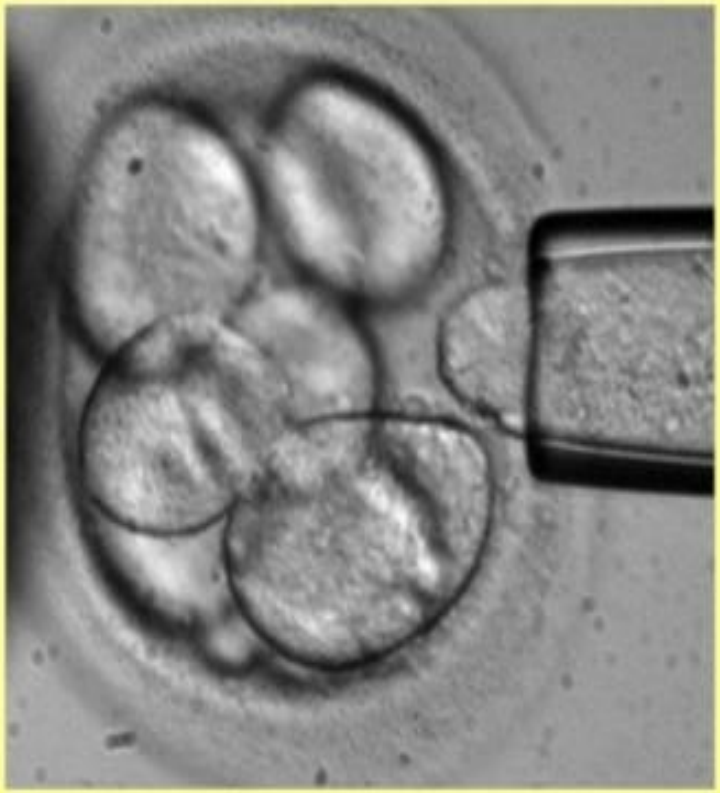


Xylem are the long trachea elements that transport water in a plant.

Phloem is part of a plant that carries food down the stem, and carries sugar, and protein to all parts of the plant that need them.

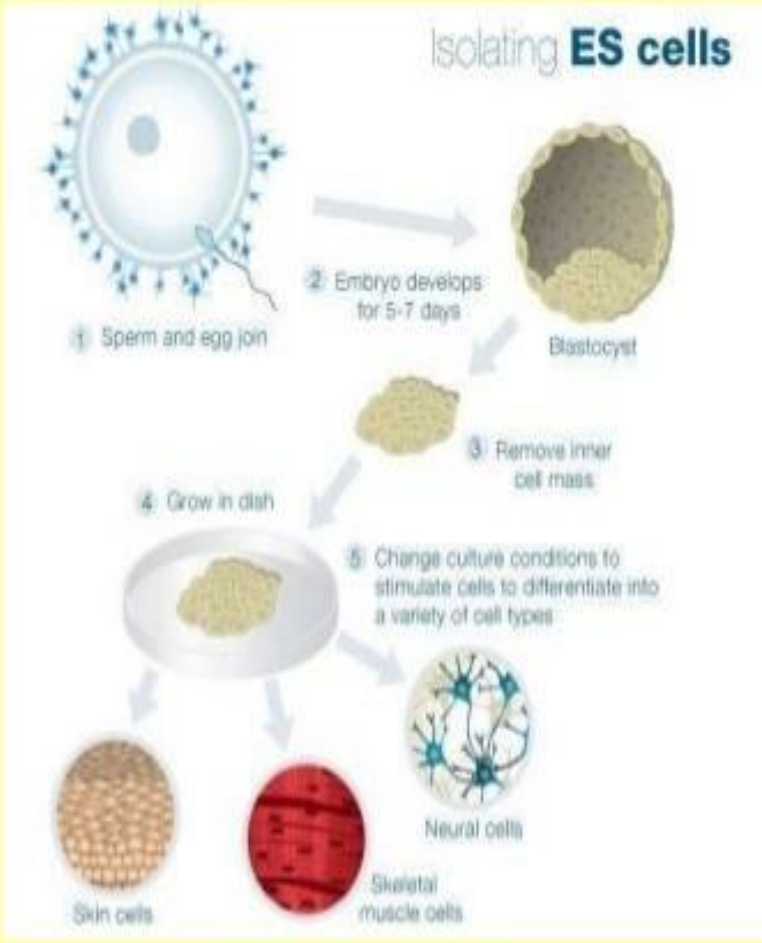
Stem Cells

- Internal repair syste
  - divide without limit, to replenish other cells as long as the organism is living.
- When a stem cell divides, each new cell has the potential either to remain a stem cell or become another type of cell with a more specialized function:
  - i.e. muscle cell, a red blood cell, or a brain cell.
- Unspecialized but can give rise to specialized cells



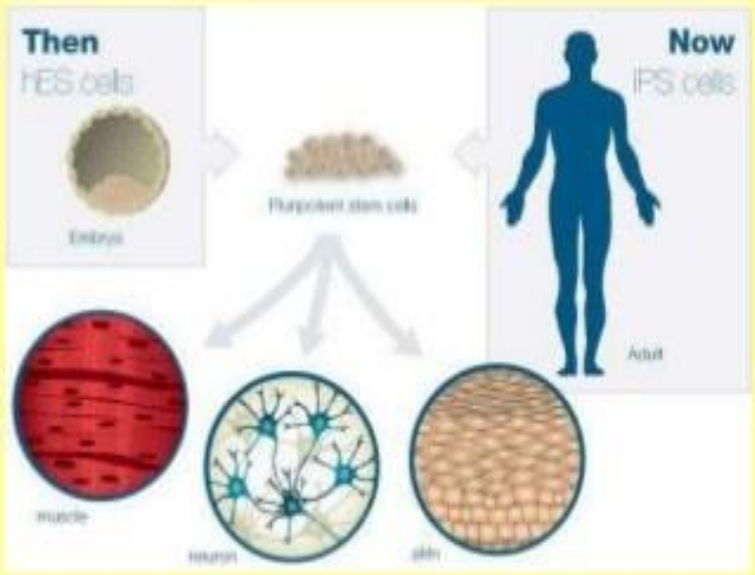
Types of Stem Cells

- Embryonic Stem Cells (ES cells)
  - derived from a four- or five-day-old human embryo in the blastocyst phase of development.
  - embryos are usually extras created in IVF (in vitro fertilization) clinics where several eggs are fertilized in a test tube
    - only one is implanted into a woman.



Types of Stem Cells

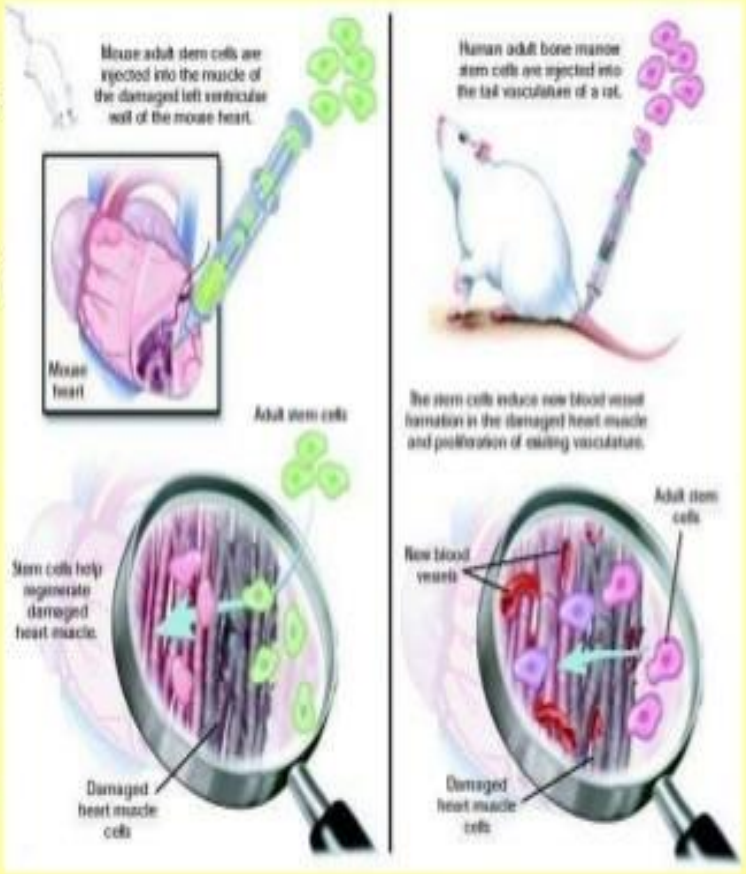
- An adult stem cell is thought to be an undifferentiated cell, found among differentiated cells in a tissue or organ that can renew itself (like bone marrow) and can differentiate to yield some or all of the major specialized cell types of the tissue or organ.



- Induced pluripotent stem cells (iPSCs) are adult cells that have been genetically reprogrammed to an embryonic stem cell–like state by being forced to express genes and factors important for maintaining the defining properties of embryonic stem cells.

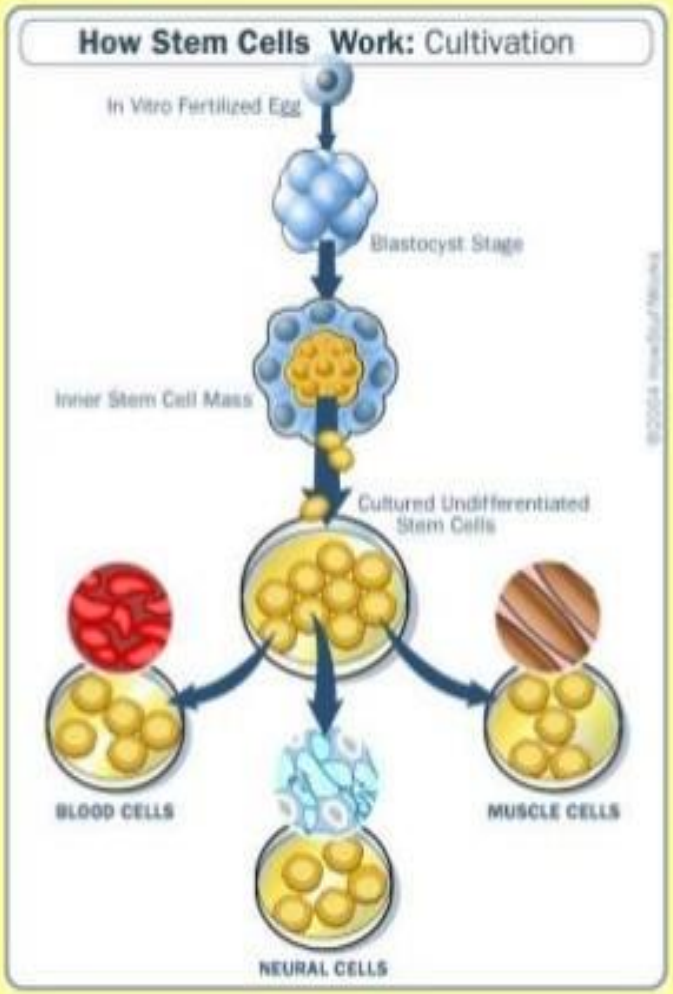
Potential Uses of Stem Cells

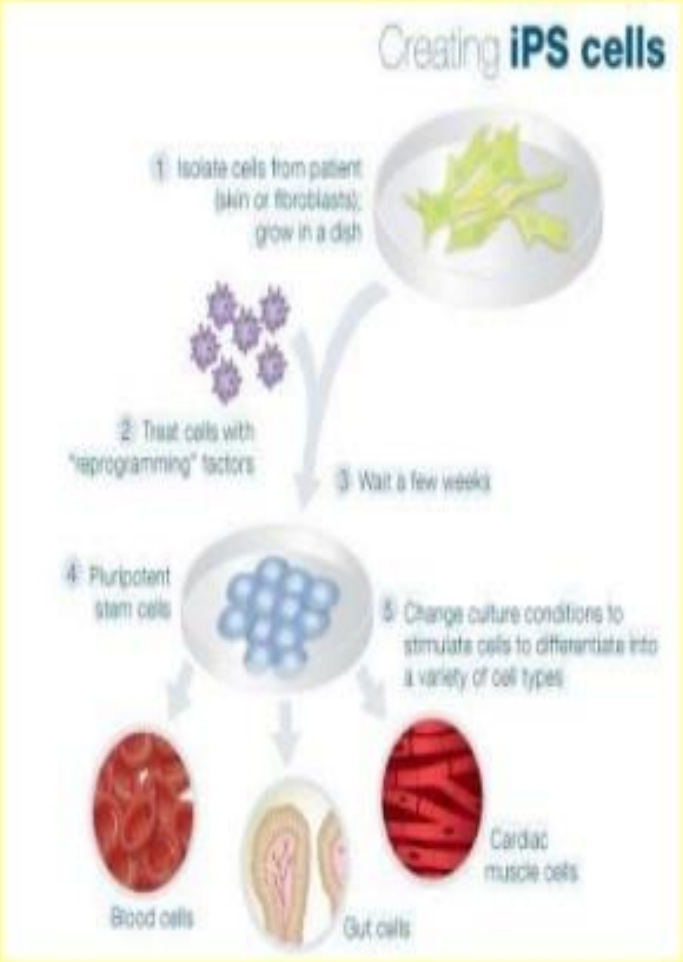
- Test new medicines
- transplantable tissues and organs
- treat diseases including Alzheimer's diseases, spinal cord injury, stroke, burns, heart disease, diabetes, osteoarthritis, rheumatoid arthritis, and cancer
- Bone marrow contains blood-forming stem cells (hematopoietic stem cells) have been used for decades to treat blood cancers and other blood disorders. Umbilical cord blood is another source of hematopoietic stem cells that is being used in treatment.
  - http://marrow.org/Physicians/When_to_Transplant/Diseases_Transplanted.aspx



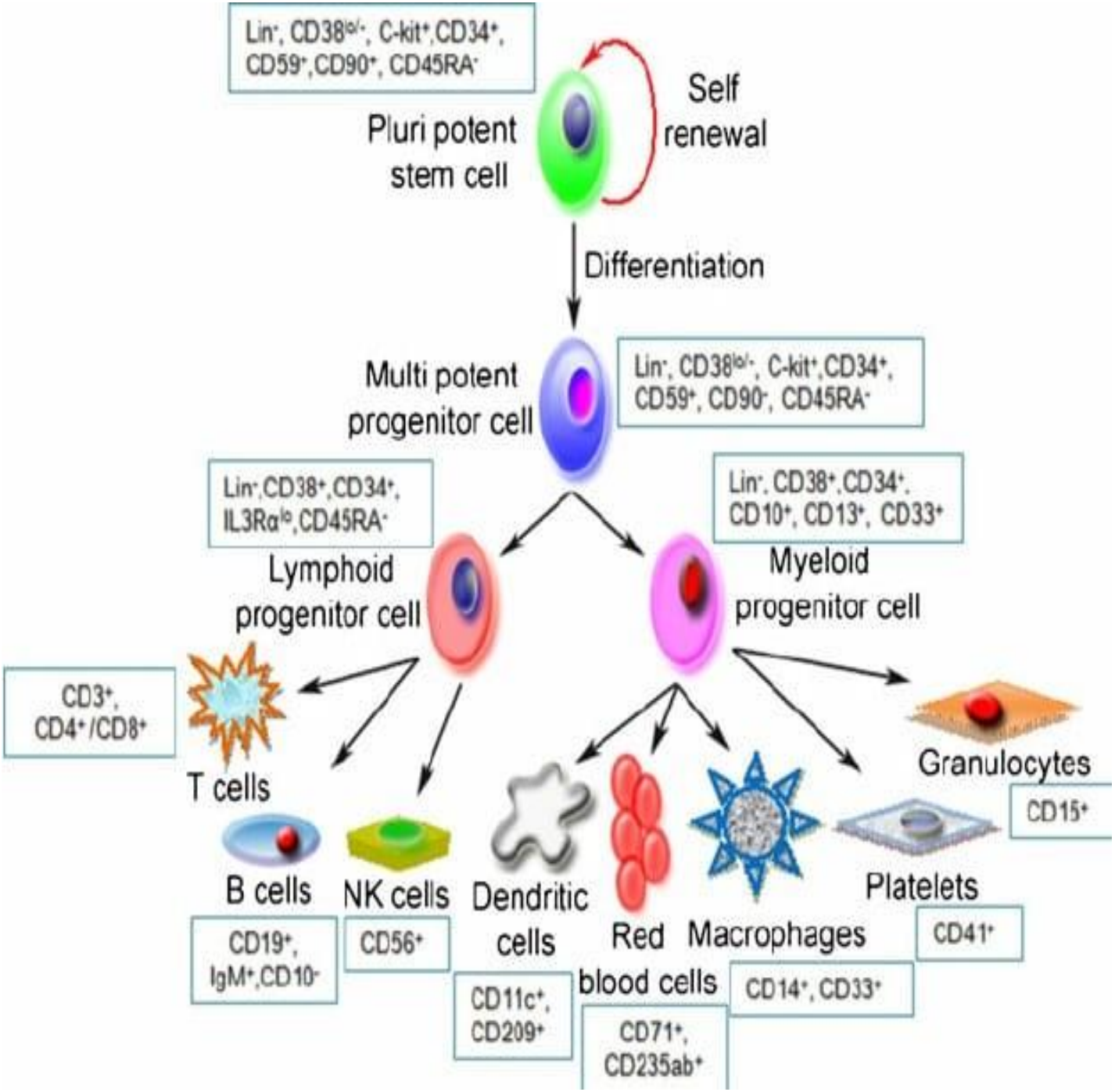
Stem Cells

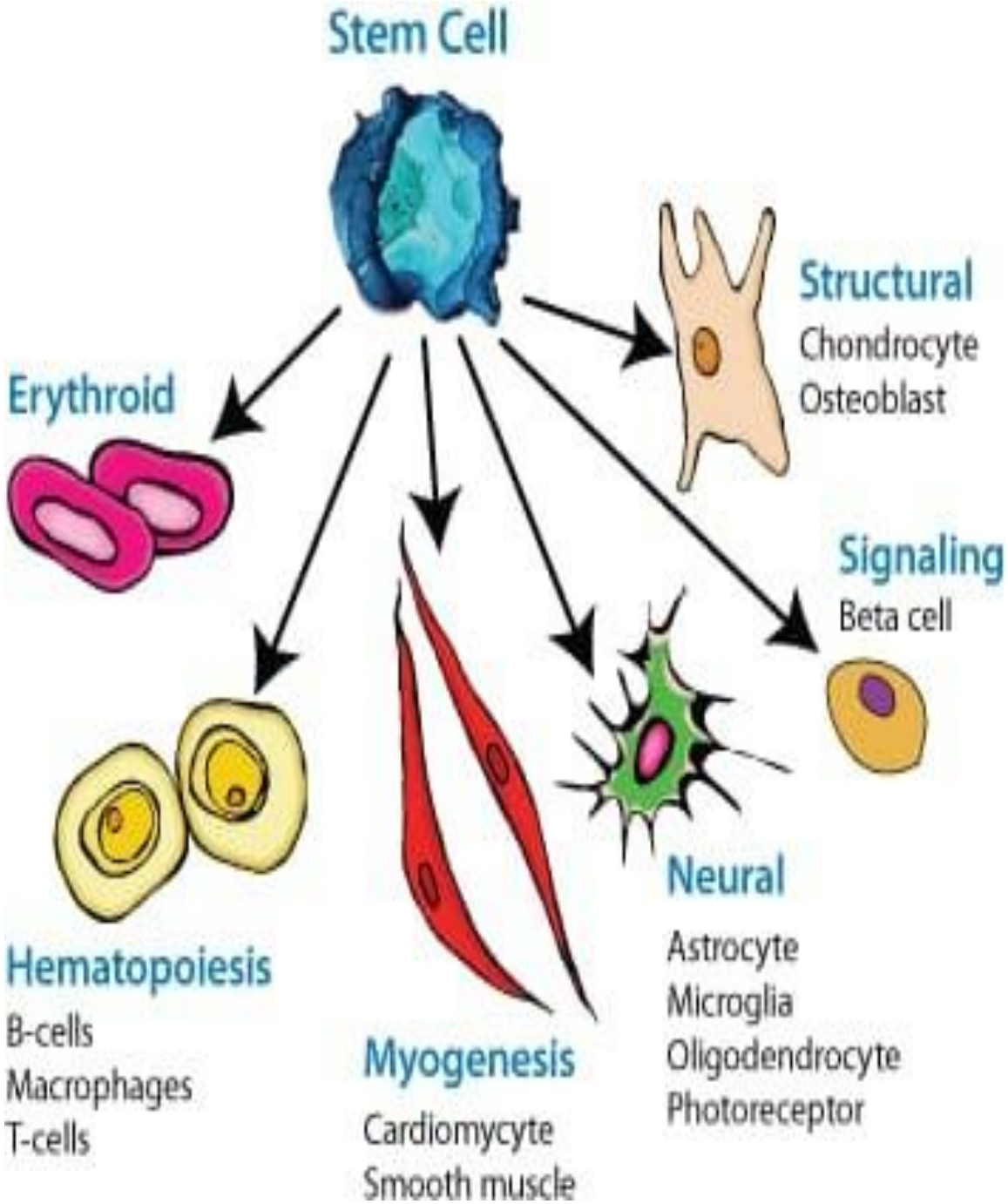
- http://learn.genetics.utah.edu/content/tech/stemcells/scintro/
- http://www.pbs.org/wgbh/nova/body/stem-cells-breakthrough.html
- http://www.youtube.com/watch?v=tJnmyBTJgkQ

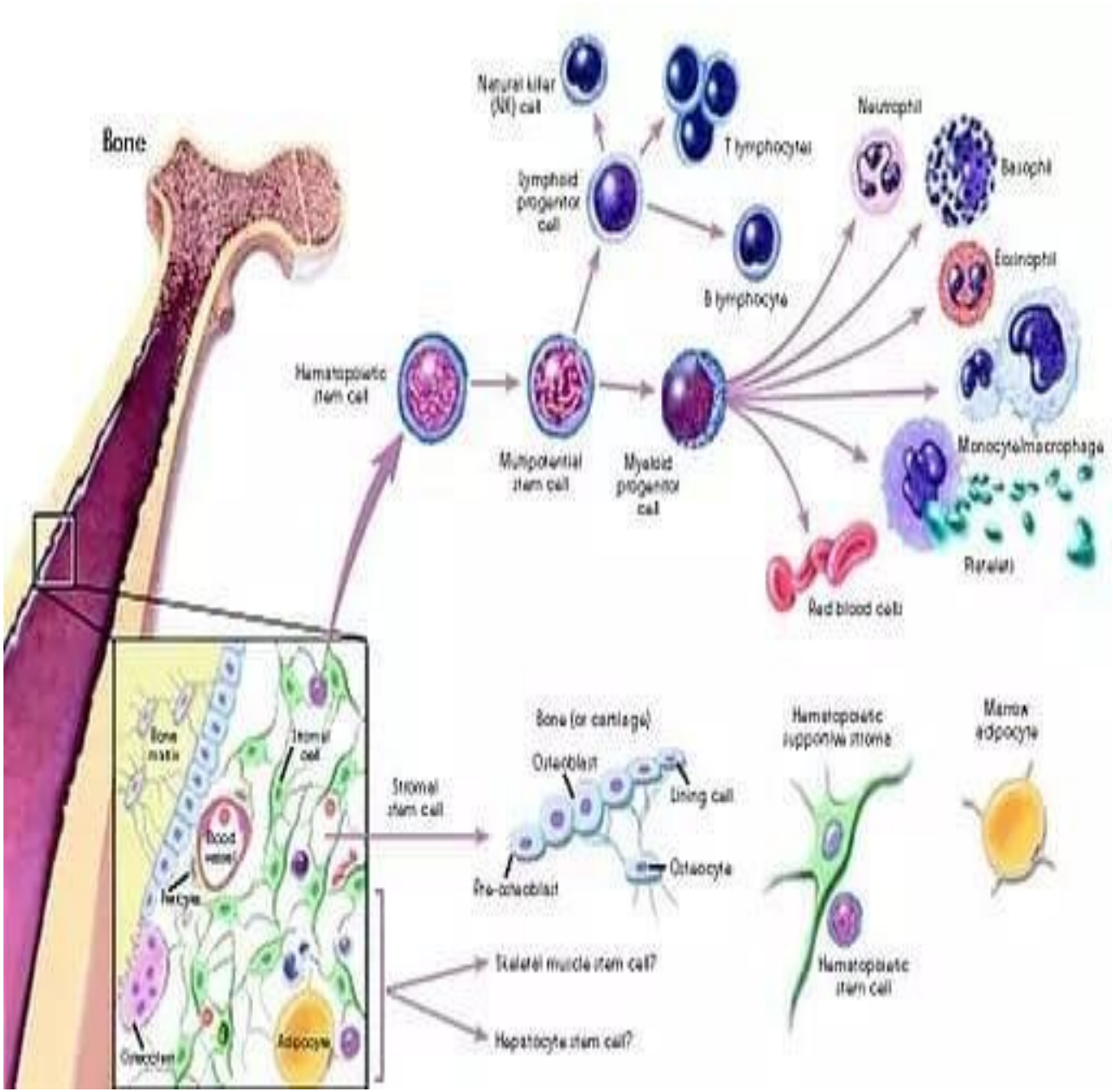




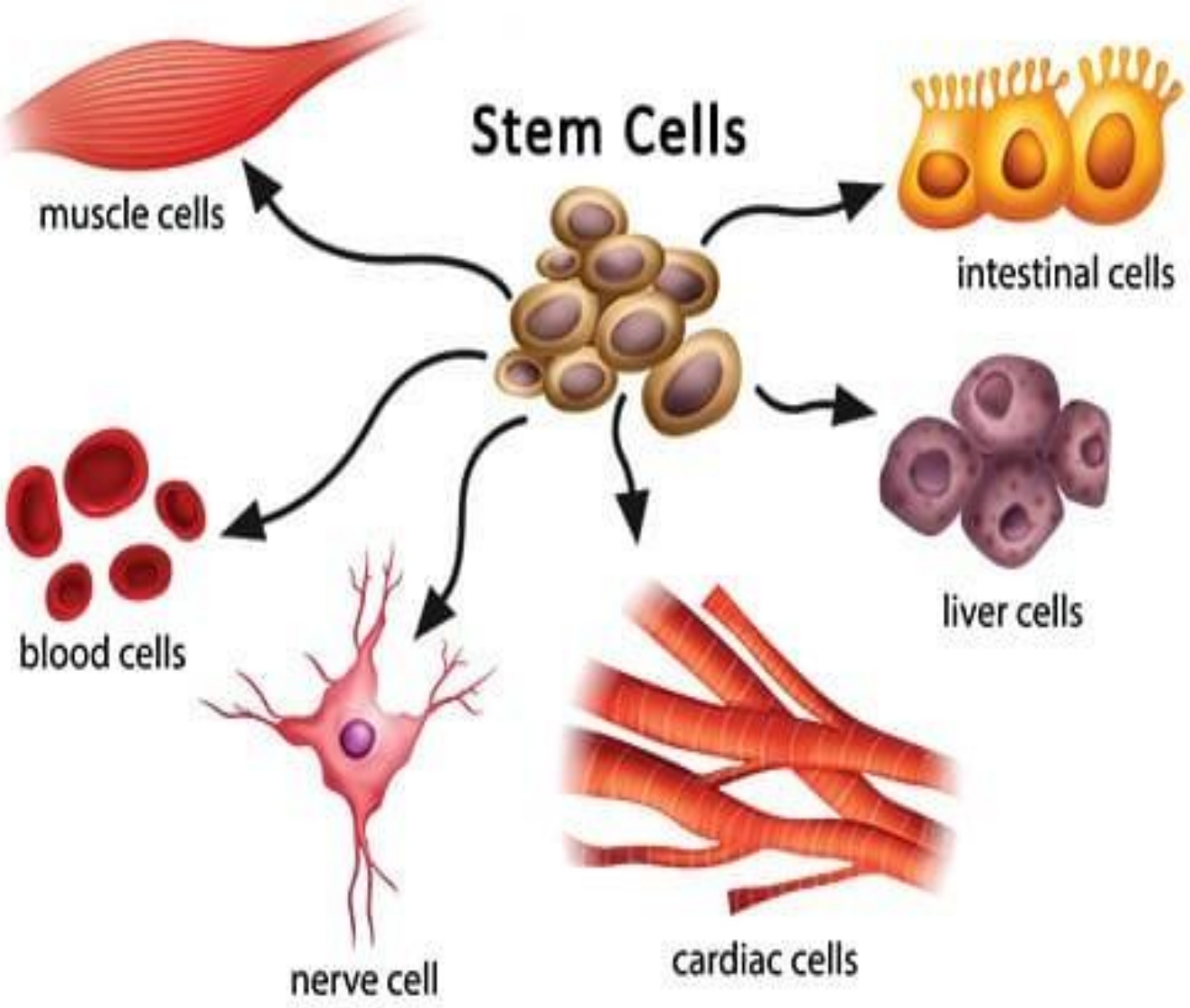
http://www.pbs.org/wgbh/nova/body/stem-cells-research.html

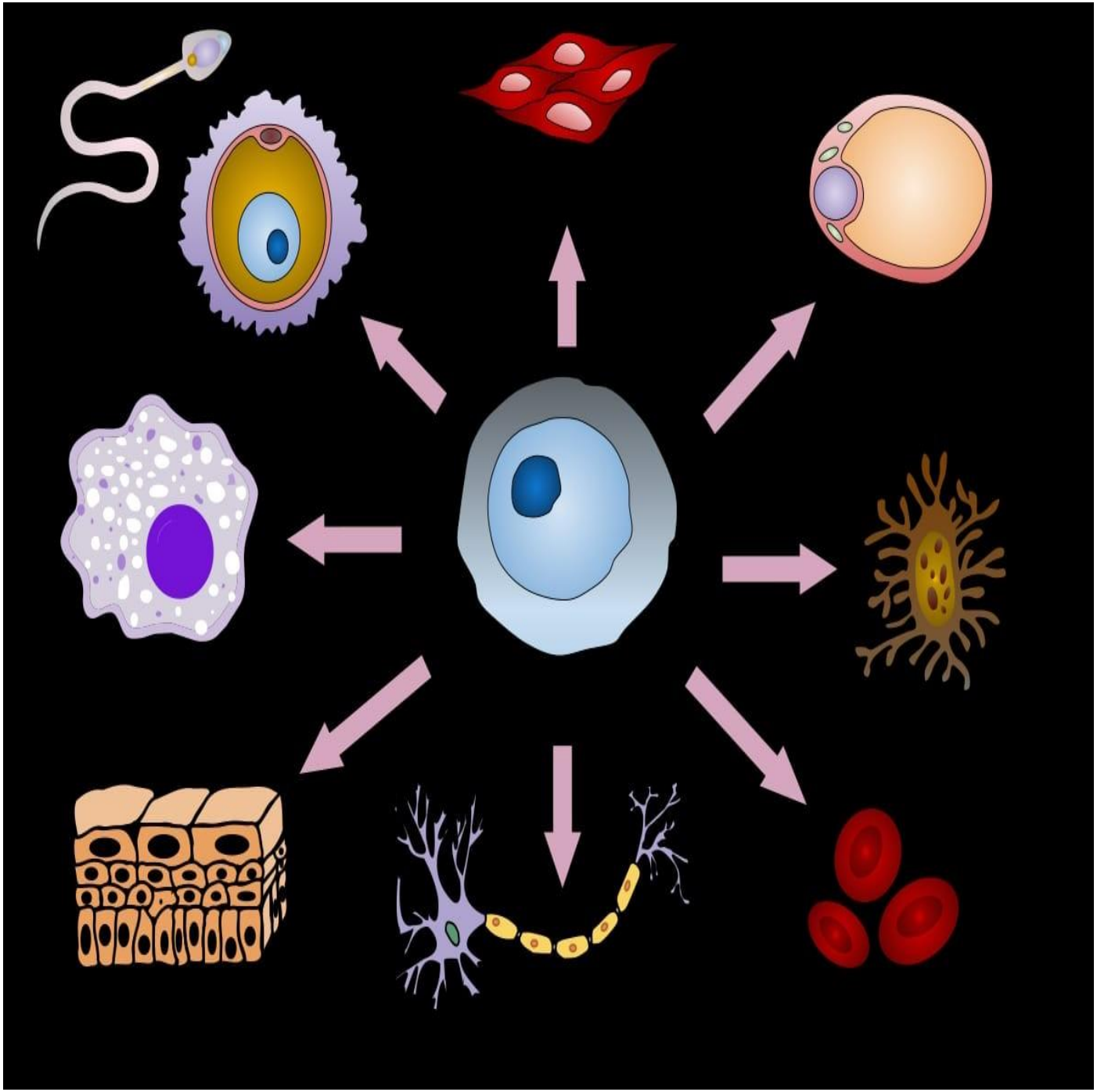

Lin-, CD38lo/-, C-kit+,CD34+, CD59+,CD90+, CD45RA-
Pluri potent stem cell
Self renewal
Differentiation
Multi potent progenitor cell
Lin-, CD38lo/-, C-kit+,CD34+, CD59+, CD90-, CD45RA-
Lin-,CD38+,CD34+, IL3Rαlo,CD45RA-
Lymphoid progenitor cell
Lin-, CD38+,CD34+, CD10+, CD13+, CD33+
Myeloid progenitor cell
CD3+, CD4+/CD8+
T cells
Granulocytes
CD15+
B cells
CD19+, IgM+,CD10-
NK cells
CD56+
Dendritic cells
CD11c+, CD209+
Red blood cells
CD71+, CD235ab+
Macrophages
CD14+, CD33+
Platelets
CD41+

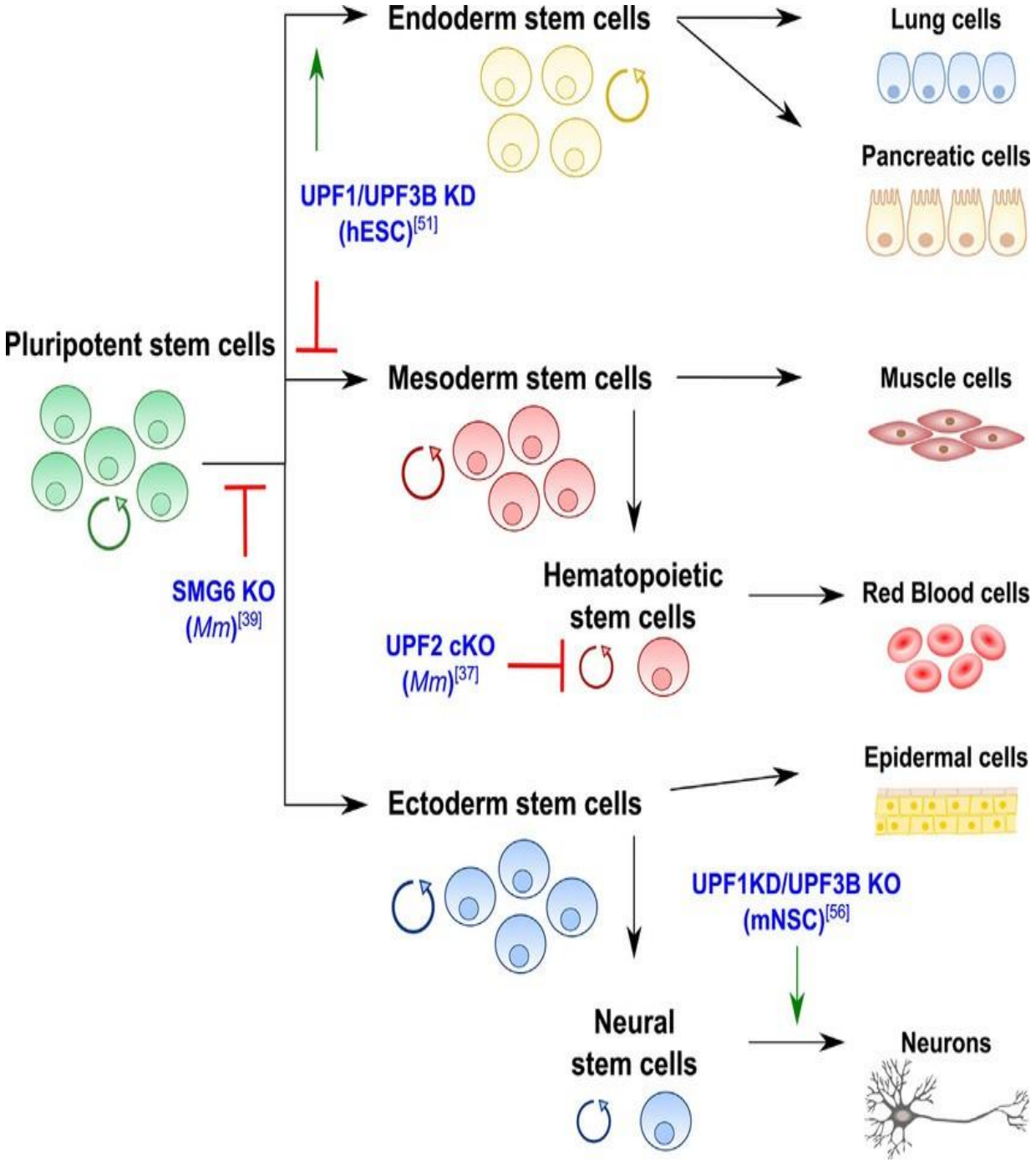

Stem Cell
Erythroid
Structural
Chondrocyte
Osteoblast
Signaling
Beta cell
Neural
Astrocyte
Microglia
Oligodendrocyte
Photoreceptor
Hematopoiesis
B-cells
Macrophages
T-cells
Myogenesis
Cardiomycyte
Smooth muscle

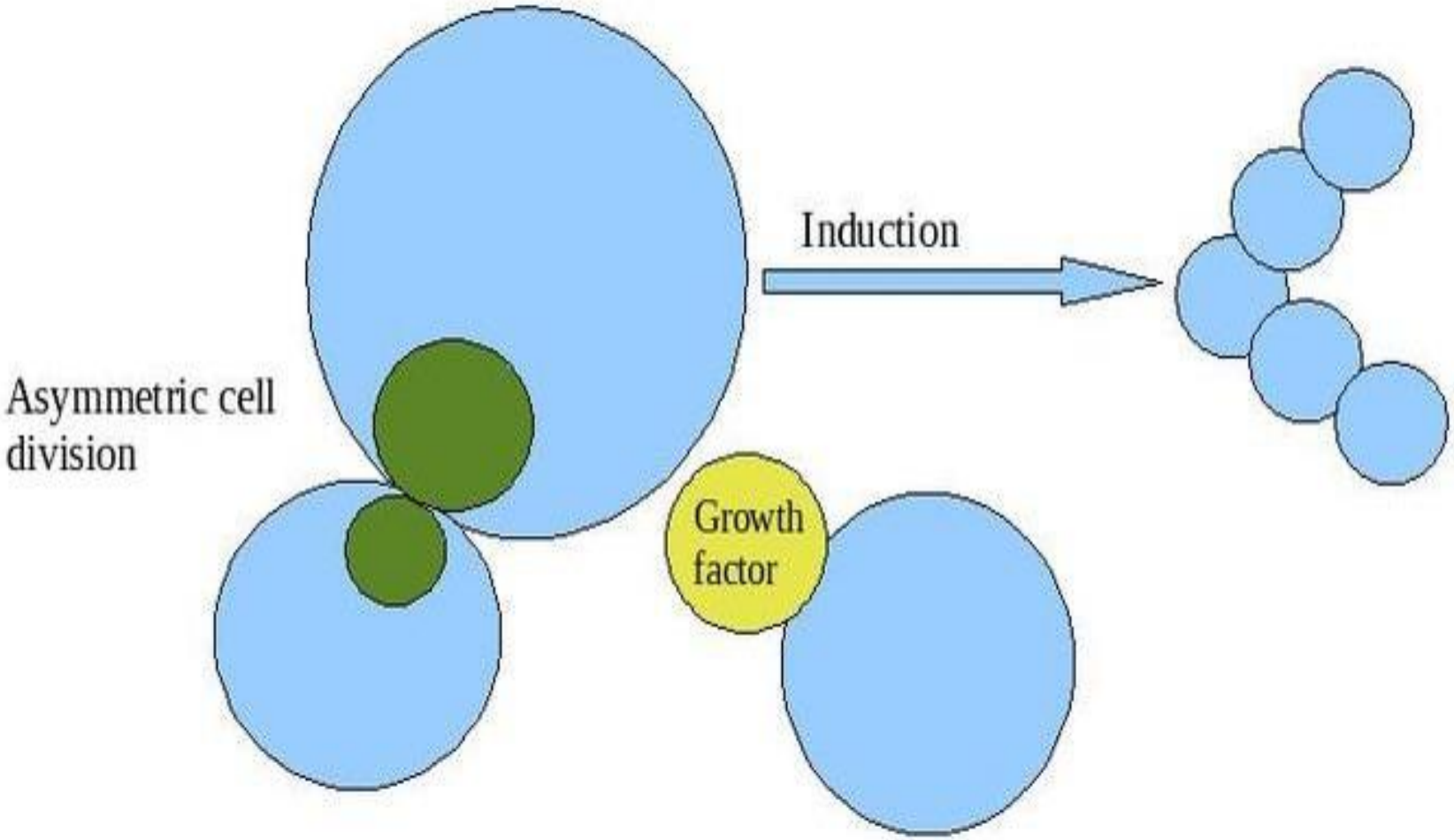

Bone
Natural killer (NK) cell
T lymphocytes
Lymphoid progenitor cell
B lymphocyte
Neutrophil
Basophil
Eosinophil
Monocyte/macrophage
Platelets
Red blood cells
Hematopoietic stem cell
Multipotential stem cell
Myeloid progenitor cell
Bone marrow
Stromal cell
Blood vessel
Nerve
Osteocyte
Adipocyte
Stromal stem cell
Bone (or cartilage)
Osteoblast
Lining cell
Osteocyte
Pre-osteoblast
Skeletal muscle stem cell?
Hepatocyte stem cell?
Hematopoietic supportive stroma
Hematopoietic stem cell
Marrow adipocyte

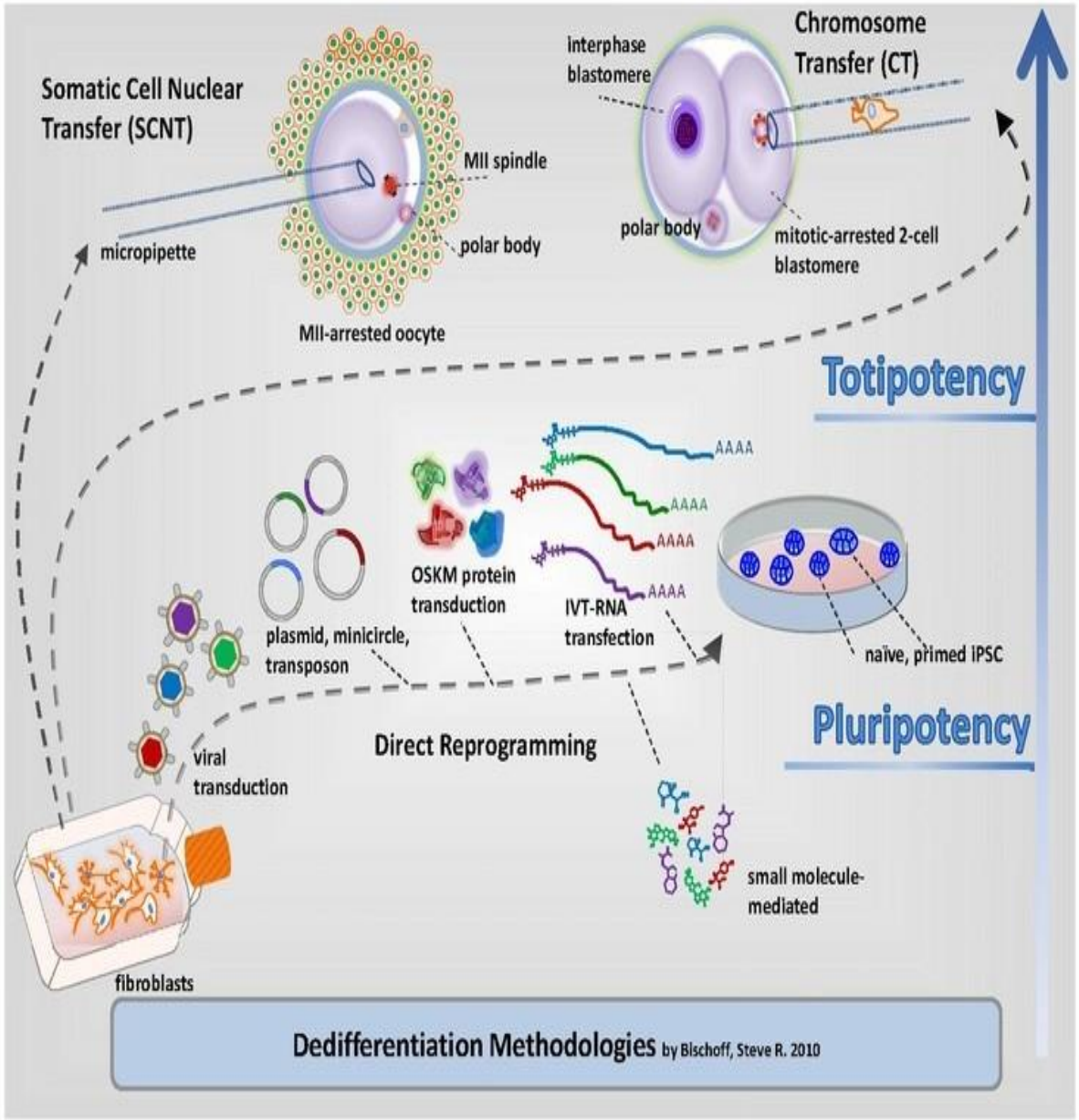
Cell Differentiation






Endoderm stem cells
Lung cells
Pancreatic cells
UPF1/UPF3B KD
(hESC)[51]
Pluripotent stem cells
Mesoderm stem cells
Muscle cells
Hematopoietic
stem cells
Red Blood cells
SMG6 KO
(Mm)[39]
UPF2 cKO
(Mm)[37]
Epidermal cells
Ectoderm stem cells
UPF1KD/UPF3B KO
(mNSC)[56]
Neural
stem cells
Neurons


Induction
Asymmetric cell division
Growth factor


Somatic Cell Nuclear Transfer (SCNT)
MII spindle
polar body
micropipette
MII-arrested oocyte
interphase blastomere
Chromosome Transfer (CT)
polar body
mitotic-arrested 2-cell blastomere
Totipotency
AAAA
AAAA
AAAA
AAAA
OSKM protein transduction
IVT-RNA transfection
plasmid, minicircle, transposon
naïve, primed IPSC
Pluripotency
Direct Reprogramming
viral transduction
small molecule-mediated
fibroblasts
Dedifferentiation Methodologies by Bischoff, Steve R. 2010

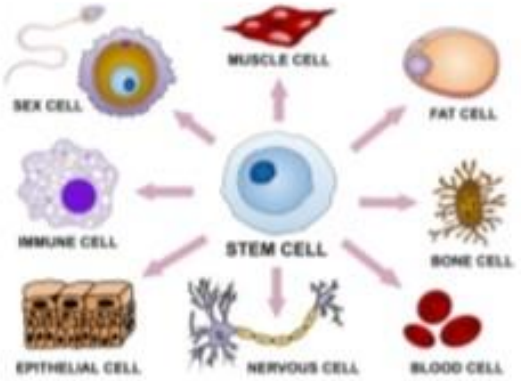
Cellular Differentiation

- Every nucleus of every cell has the same set of genes. A heart cell nucleus contains skin cell genes, as well as the genes that instruct stomach cells how to absorb nutrients.
- Therefore, for cells to differentiate, certain genes must somehow be activated, while others remain inactive.
- Genes instruct each cell how and when to build the proteins that allow it to create the structures, and ultimately perform the functions, specific to its type of cell.

Cellular Differentiation

- Each of us originated as a single, simple-looking cell -- a fertilized egg, or zygote -- so tiny that it can barely be seen without a microscope. (*A human egg cell is about 1/100th of a centimetre in diameter, or a bit smaller than the width of a human hair.*)
- Shortly after fertilization, the zygote begins dividing, replicating itself again and again. Before long, a growing mass, or blastula, of dozens, then hundreds, then thousands of cells called stem cells forms; each stem cell is only one-fourth to one-tenth the diameter of the original zygote, but otherwise nearly identical to it

Cellular differentiation



Stem cell differentiation into various tissue types.

Differentiation continues in adulthood as adult stem cells divide and create fully differentiated daughter cells during tissue repair and during normal cell turnover. Some differentiation occurs in response to antigen exposure. Differentiation dramatically changes a cell's size, shape, membrane potential, metabolic activity, and responsiveness to signals. These changes are largely due to highly controlled modifications in gene expression and are the study of epigenetics. With a few exceptions, cellular differentiation almost never involves a change in the DNA sequence itself. Thus, different cells can

have very different physical characteristics despite having the same genome.

A specialized type of differentiation, known as 'terminal differentiation', is of importance in some tissues, for example vertebrate nervous system, striated muscle, epidermis and gut. During terminal differentiation, a precursor cell formerly capable of cell division, permanently leaves the cell cycle, dismantles the cell cycle machinery and often expresses a range of genes characteristic of the cell's final function (e.g. myosin and actin for a muscle cell). Differentiation may continue to occur after terminal differentiation if the

capacity and functions of the cell undergo further changes.

Among dividing cells, there are multiple levels of cell potency, the cell's ability to differentiate into other cell types. A greater potency indicates a larger number of cell types that can be derived. A cell that can differentiate into all cell types, including the placental tissue, is known as ***totipotent***. In mammals, only the zygote and subsequent blastomeres are totipotent, while in plants, many differentiated cells can become totipotent with simple laboratory techniques. A cell that can differentiate into all cell types of the adult organism is

known as ***pluripotent***. Such cells are called meristematic cells in higher plants and embryonic stem cells in animals, though some groups report the presence of adult pluripotent cells. Virally induced expression of four transcription factors Oct4, Sox2, c-Myc, and Klf4 (Yamanaka factors) is sufficient to create pluripotent (iPS) cells from adult fibroblasts.[4] A multipotent cell is one that can differentiate into multiple different, but closely related cell types.[5] Oligopotent cells are more restricted than multipotent, but can still differentiate into a few closely related cell types.[5] Finally, unipotent cells can differentiate into only one cell type, but are capable of self-

Mammalian cell types

Three basic categories of cells make up the mammalian body: germ cells, somatic cells, and stem cells. Each of the approximately 37.2 trillion (3.72×10^{13}) cells in an adult human has its own copy or copies of the genome except certain cell types, such as red blood cells, that lack nuclei in their fully differentiated state. Most cells are diploid; they have two copies of each chromosome. Such cells, called somatic cells, make up most of the human body, such as skin and muscle cells. Cells differentiate to specialize for different functions.[Z]

Development begins when a sperm fertilizes an egg and creates a single cell that has the potential to form an entire organism. In the first hours after fertilization, this cell divides into identical cells. In humans, approximately four days after fertilization and after several cycles of cell division, these cells begin to specialize, forming a hollow sphere of cells, called a blastocyst.[8] The blastocyst has an outer layer of cells, and inside this hollow sphere, there is a cluster of cells called the inner cell mass. The cells of the inner cell mass go on to form virtually all of the tissues of the human body. Although the cells of the inner cell mass can form virtually every

type of cell found in the human body, they cannot form an organism. These cells are referred to as pluripotent.[9]

Pluripotent stem cells undergo further specialization into multipotent progenitor cells that then give rise to functional cells. Examples of stem and progenitor cells include:

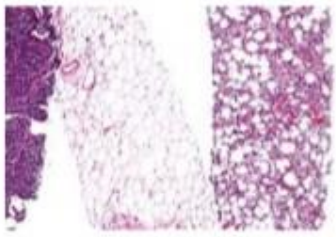
- *Radial glial cells* (embryonic neural stem cells) that give rise to excitatory neurons in the fetal brain through the process of neurogenesis.[10][11][12]
- *Hematopoietic stem cells* (adult stem cells) from the bone marrow that give

rise to red blood cells, white blood cells, and platelets

- *Mesenchymal stem cells* (adult stem cells) from the bone marrow that give rise to stromal cells, fat cells, and types of bone cells
- *Epithelial stem cells* (progenitor cells) that give rise to the various types of skin cells
- *Muscle satellite cells* (progenitor cells) that contribute to differentiated muscle tissue.

A pathway that is guided by the cell adhesion molecules consisting of four amino acids, arginine, glycine, asparagine,

Dedifferentiation



Micrograph of a liposarcoma with some dedifferentiation, that is not identifiable as a liposarcoma, (left edge of image) and a differentiated component (with lipoblasts and increased vascularity (right of image)). Fully differentiated (morphologically benign) adipose tissue (center of the image) has few blood vessels. H&E stain.

Dedifferentiation, or integration is a cellular process often seen in more basal life forms such as worms and amphibians in which a partially or terminally differentiated cell reverts to an earlier developmental stage, usually as part of a regenerative

process.[13][14] Dedifferentiation also occurs in plants.[15] Cells in cell culture can lose properties they originally had, such as protein expression, or change shape. This process is also termed dedifferentiation.[16]

Some believe dedifferentiation is an aberration of the normal development cycle that results in cancer,[17] whereas others believe it to be a natural part of the immune response lost by humans at some point as a result of evolution.

A small molecule dubbed reversine, a purine analog, has been discovered that has proven to induce dedifferentiation in

myotubes. These dedifferentiated cells could then redifferentiate into osteo[illegible] and adipocytes.[18]

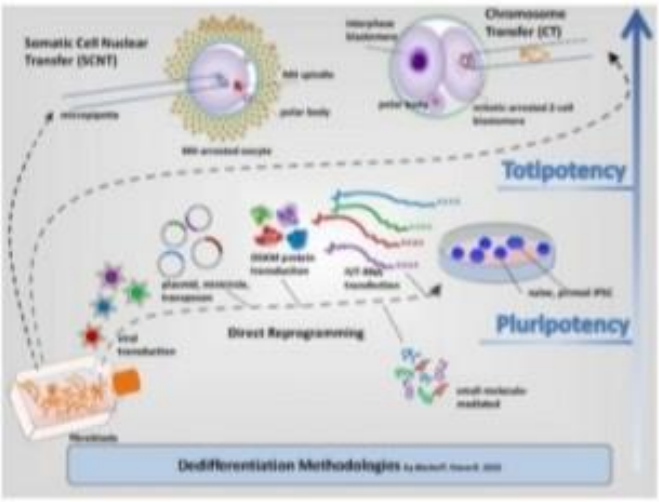
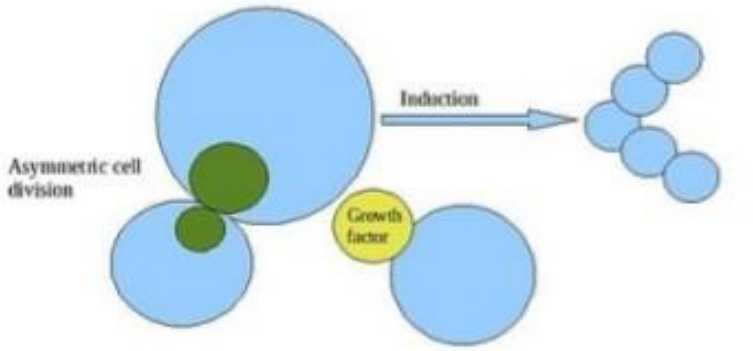


Diagram exposing several methods used to revert adult somatic cells to totipotency or pluripotency.

Mechanisms

Mechanisms

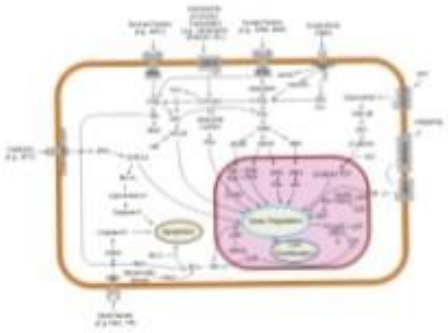


Mechanisms of cellular differentiation.

Each specialized cell type in an organism expresses a subset of all the genes that constitute the genome of that species. Each cell type is defined by its particular pattern of regulated gene expression. Cell differentiation is thus a transition of a cell from one cell type to another and it involves

differentiation during development can be understood as the result of a gene regulatory network. A regulatory gene and its cis-regulatory modules are nodes in a gene regulatory network; they receive input and create output elsewhere in the network.[19] The systems biology approach to developmental biology emphasizes the importance of investigating how developmental mechanisms interact to produce predictable patterns (morphogenesis). However, an alternative view has been proposed recently. Based on stochastic gene expression, cellular differentiation is the result of a Darwinian selective process occurring among cells. In

this frame, protein and gene networks are the result of cellular processes and not their cause.



An overview of major signal transduction pathways.

While evolutionarily conserved molecular processes are involved in the cellular mechanisms underlying these switches, in animal species these are very different from the well-characterized gene regulatory mechanisms of bacteria, and even from

those of the animals' closest unicellular relatives.[20] Specifically, cell differentiation in animals is highly dependent on biomolecular condensates of regulatory proteins and enhancer DNA sequences.

Cellular differentiation is often controlled by cell signaling. Many of the signal molecules that convey information from cell to cell during the control of cellular differentiation are called growth factors. Although the details of specific signal transduction pathways vary, these pathways often share the following general steps. A ligand produced by one cell binds to a receptor in the extracellular region of another cell,

inducing a conformational change in the receptor. The shape of the cytoplasmic domain of the receptor changes, ai receptor acquires enzymatic activity. The receptor then catalyzes reactions that phosphorylate other proteins, activating them. A cascade of phosphorylation reactions eventually activates a dormant transcription factor or cytoskeletal protein, thus contributing to the differentiation process in the target cell.[21] Cells and tissues can vary in competence, their ability to respond to external signals.[22]

Signal induction refers to cascades of signaling events, during which a cell or

tissue signals to another cell or tissue to influence its developmental fate.[22] Yamamoto and Jeffery[23] investigated the role of the lens in eye formation in c and surface-dwelling fish, a striking example of induction.[22] Through reciprocal transplants, Yamamoto and Jeffery[23] found that the lens vesicle of surface fish can induce other parts of the eye to develop in cave- and surface-dwelling fish, while the lens vesicle of the cave-dwelling fish cannot.[22]

Other important mechanisms fall under the category of asymmetric cell divisions, divisions that give rise to daughter cells

with distinct developmental fates. Asymmetric cell divisions can occur because of asymmetrically expres maternal **cytoplasmic determinants** or because of signaling.[22] In the former mechanism, distinct daughter cells are created during cytokinesis because of an uneven distribution of regulatory molecules in the parent cell; the distinct cytoplasm that each daughter cell inherits results in a distinct pattern of differentiation for each daughter cell. A well-studied example of pattern formation by asymmetric divisions is body axis patterning in Drosophila. RNA molecules are an important type of intracellular differentiation control signal.

The molecular and genetic basis of asymmetric cell divisions has also been studied in green algae of the genus *Volvox*, a model system for studying how unicellular organisms can evolve into multicellular organisms.[22] In *Volvox carteri*, the 16 cells in the anterior hemisphere of a 32-cell embryo divide asymmetrically, each producing one large and one small daughter cell. The size of the cell at the end of all cell divisions determines whether it becomes a specialized germ or somatic cell.[22][24]

Epigenetic control

Since each cell, regardless of cell type, possesses the same genome, determination of cell type must occur at the level of gene expression. While the regulation of gene expression can occur through cis- and trans-regulatory elements including a gene's promoter and enhancers, the problem arises as to how this expression pattern is maintained over numerous generations of cell division. As it turns out, epigenetic processes play a crucial role in regulating the decision to adopt a stem, progenitor, or mature cell fate. This section will focus primarily on mammalian stem cells.

Importance of epigenetic control

The first question that can be asked is the extent and complexity of the role of epigenetic processes in the determination of cell fate. A clear answer to this question can be seen in the 2011 paper by Lister R, *et al.* [26] on aberrant epigenomic

programming in human induced pluripotent stem cells. As induced pluripotent stem cells (iPSCs) are thought to mimic embryonic stem cells in their pluripotent properties, few epigenetic differences should exist between them. To test this prediction, the authors conducted whole-genome profiling of DNA methylation patterns in several human embryonic stem cell (ESC), iPSC, and progenitor cell lines.

Female adipose cells, lung fibroblasts, and foreskin fibroblasts were reprogrammed into induced pluripotent state with the

iPSCs, somatic cells were compared. Lister R, ***et al.*** observed significant resemblance in methylation levels between embryonic and induced pluripotent cells. Around 80% of CG dinucleotides in ESCs and iPSCs were methylated, the same was true of only 60% of CG dinucleotides in somatic cells. In addition, somatic cells possessed minimal levels of cytosine methylation in non-CG dinucleotides, while induced pluripotent cells possessed similar levels of methylation as embryonic stem cells, between 0.5 and 1.5%. Thus, consistent with their respective transcriptional activities,[26] DNA methylation patterns, at

selection.[28] Increased levels of Oct4 and decreased levels of Sox2 promote a mesendodermal fate, with Oct4 actively suppressing genes associated with a neural ectodermal fate. Similarly, Increased levels of Sox2 and decreased levels of Oct4 promote differentiation towards a neural ectodermal fate, with Sox2 inhibiting differentiation towards a mesendo fate. Regardless of the lineage cells differentiate down, suppression of NANOG has been identified as a necessary prerequisite for differentiation.[28]

Role of signaling in epigenetic control

A final question to ask concerns the role of cell signaling in influencing the epigenetic processes governing differentiation. Such a

role should exist, as it would be reasonable to think that extrinsic signaling can lead to epigenetic remodeling, just as it can lead to changes in gene expression through the activation or repression of different transcription factors. Little direct dat

available concerning the specific signals that influence the epigenome, and the majority of current knowledge about the subject consists of speculations on plausible candidate regulators of epigenetic remodeling.[38] We will first discuss several major candidates thought to be involved in the induction and maintenance of both embryonic stem cells and their differentiated progeny, and then turn to one

Growth factors comprise the second major set of candidates of epigenetic regulators of cellular differentiation. These morphogens are crucial for development, and include bone morphogenetic proteins, transforming growth factors (TGFs), and fibroblast growth factors (FGFs). TGFs and FGFs have been shown to sustain expression of OCT4, SOX2, and NANOG by downstream signaling to Smad proteins.[38] Depletion of growth factors promotes the differentiation of ESCs, while genes in bivalent chromatin can become either more restrictive or permissive in their transcription.[38]

Several other signaling pathways are also considered to be primary candidates. Cytokine leukemia inhibitory factors are associated with the maintenance of mouse ESCs in an undifferentiated state. This is achieved through its activation of the Jak-STAT3 pathway, which has been shown to be necessary and sufficient towards maintaining mouse ESC pluripotency.[39] Retinoic acid can induce differentia 45/75 human and mouse ESCs,[38] and Notch signaling is involved in the proliferation and self-renewal of stem cells. Finally, Sonic hedgehog, in addition to its role as a morphogen, promotes embryonic stem cell

example of specific signaling pathways in which more direct evidence exists for its role in epigenetic change.

The first major candidate is Wnt signaling pathway. The Wnt pathway is involved in all stages of differentiation, and the ligand Wnt3a can substitute for the overexpression of c-Myc in the generation of induced pluripotent stem cells.[38] On the other hand, disruption of ß-catenin, a component of the Wnt signaling pathway, leads to decreased proliferation of progenitors.

THANK YOU ALL

Protein synthesis

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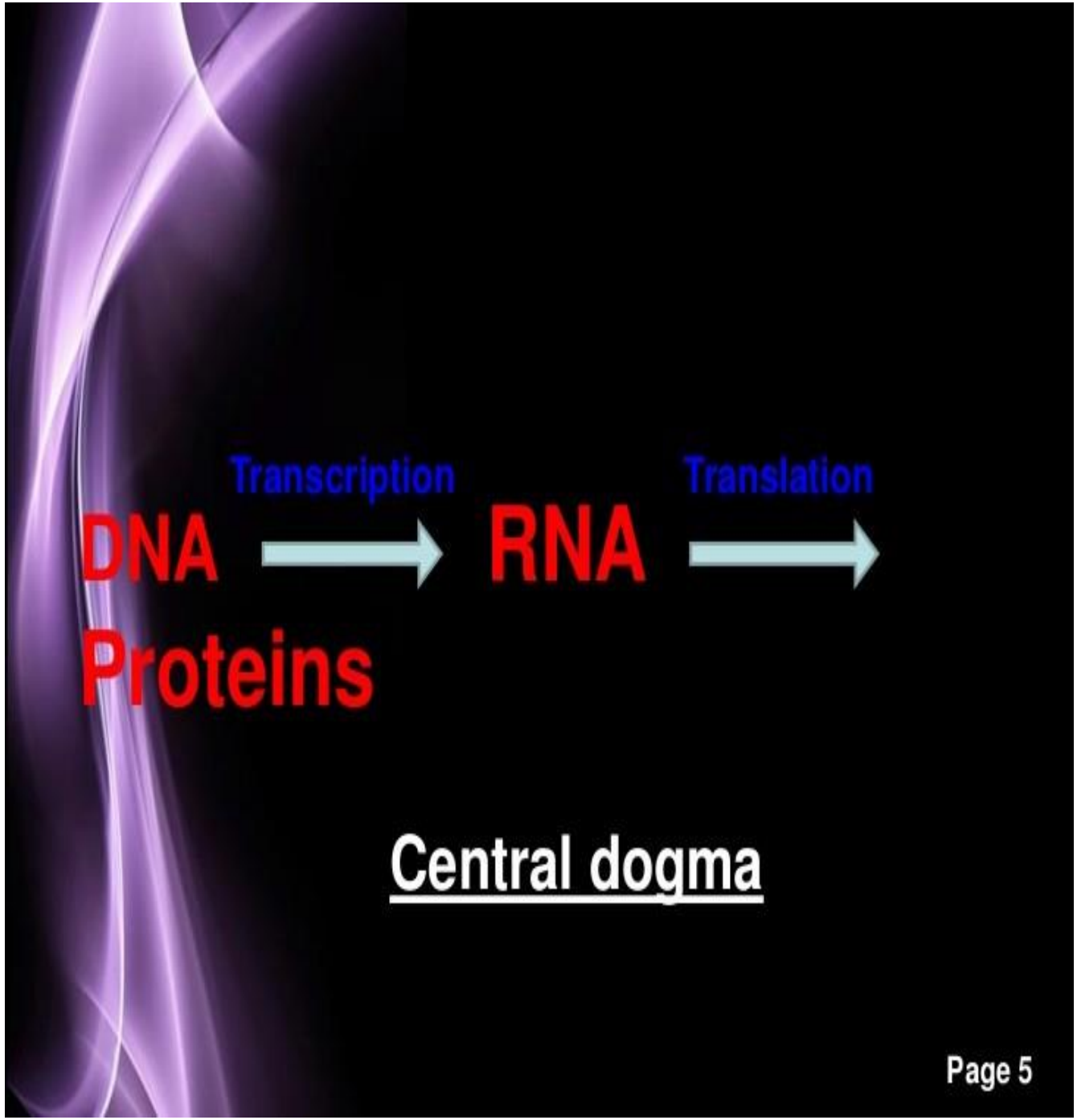
- Transcription
- Genetic code
- tRNA
- Ribosomes
- Translation
- Polyribosomes

Transcription

- **Transcription**, or RNA synthesis, is the process of creating an equivalent RNA copy of a sequence of DNA.

- Both RNA and DNA are nucleic acids, which use base pairs of nucleotides as a complementary language that can be converted back and forth from DNA to RNA in the presence of the correct enzymes.


Transcription
Translation
DNA
RNA
Proteins
Central dogma

- During transcription, a DNA sequence is read by RNA polymerase, which produces a complementary, antiparallel RNA strand.

- As opposed to DNA replication, transcription results in an RNA compliment that includes uracil (U) in all instances where thymine (T) would have occurred in a DNA compliment.

- **Transcription** is the first step leading to **gene expression.**

- The stretch of DNA transcribed into an RNA molecule is called a ***transcription unit*** and encodes at least one gene.

- If the gene transcribed encodes for a protein, the result of transcription is messenger RNA (mRNA), which will then be used to create that protein via the process of translation.

- Alternatively, the transcribed gene may encode for either ribosomal RNA (rRNA) or transfer RNA (tRNA), other components of the protein-assembly process, or other ribozymes.

A DNA transcription unit encoding for a protein contains not only the sequence that will eventually be directly translated into the protein (the *coding sequence*) but also *regulatory sequences* that direct and regulate the synthesis of that protein.

- As in DNA replication, DNA is read from 3' → 5' during transcription. Meanwhile, the complementary RNA is created from the 5' → 3' direction.

- Only one of the two DNA strands, called the template strand, is used for transcription.

- The other DNA strand is called the coding strand, because its sequence is the same as the newly created RNA transcript (except for the substitution of uracil for thymine).

- Transcription is divided into 3 stages:

1. *initiation*
2. *elongation*
3. *termination.*

Initiation

- In bacteria, transcription begins with the binding of RNA polymerase to the promoter in DNA.
- RNA polymerase is a core enzyme consisting of five subunits: 2 α subunits, 1 β subunit, 1 β' subunit, and 1 ω subunit.
- At the start of initiation, the core enzyme is associated with a sigma factor that aids in finding the appropriate -35 and -10 base pairs downstream of promoter sequences.

Elongation

- One strand of DNA, the *template strand* (or noncoding strand), is used as a template for RNA synthesis.
- As transcription proceeds, RNA polymerase traverses the template strand and uses base pairing complementarity with the DNA template to create an RNA copy.
- Although RNA polymerase traverses the template strand from 3' → 5', the coding (non-template) strand and newly-formed RNA can also be used as reference points, so transcription can be described as occurring 5' → 3'.

- This produces an RNA molecule from 5' → 3', an exact copy of the coding strand (except that thymines are replaced with uracils, and the nucleotides are composed of a ribose (5-carbon) sugar where DNA has deoxyribose (one less oxygen atom) in its sugar-phosphate backbone).

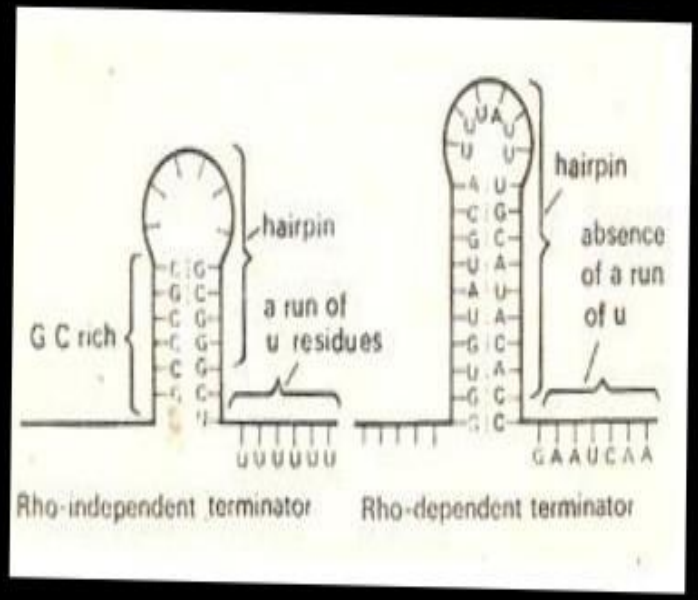
- Unlike DNA replication, mRNA transcription can involve multiple RNA polymerases on a single DNA template and multiple rounds of transcription (amplification of particular mRNA), so many mRNA molecules can be rapidly produced from a single copy of a gene.

- Elongation also involves a proofreading mechanism that can replace incorrectly incorporated bases.

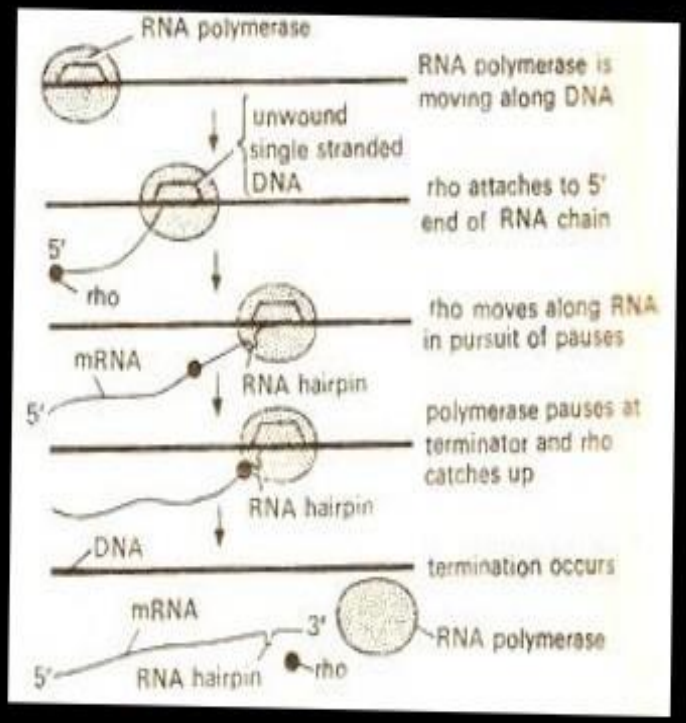
Termination

- Bacteria use two different strategies for transcription termination: Rho-independent and Rho-dependent

In **Rho-independent transcription** termination, RNA transcription stops when the newly synthesized RNA molecule forms a G-C rich hairpin loop followed by a run of U's, which makes it detach from the DNA template.



In the "Rho-dependent" type of termination, a protein factor called "Rho" destabilizes the interaction between the template and the mRNA, thus releasing the newly synthesized mRNA from the elongation complex.



Genetic code

Properties of genetic code

- **The code is universal.** All prokaryotic and eukaryotic organisms use the same codon to specify each amino acid.

- **The code is triplet.** Three nucleotides make one codon. 61 of them code for amino acids and 3 viz., UAA, UAG and UGA are nonsense codons or chain termination codons.

- **The code is degenerate.** For a particular amino acid more than one word can be used

- **The code is non overlapping.** A base in mRNA is not used for two different codons

- **The code is commaless.** There is no special signal or commas between codons.

- **The code is non ambiguous.** A particular codon will always code for the same amino acid, wherever it is found.

The Genetic Code

	U	C	A	G	
U	UUU Phenyl alanine UUC UUG Leucine UUA	UCU UCC UCA Serine UCG	UAU Tyrosine UAC UAA Stop UAG	UGU Cysteine UGC UGA Stop UGG Tryptophan	U C A G
C	CUU CUC CUA Leucine CUG	CCU CCC CCA Proline CCG	CAU Histidine CAC CAA Glutamine CAG	CGU CGC CGA Arginine CGG	U C A G
A	AUU AUC Isoleucine AUA AUG Methionine	ACU ACC ACA Threonine ACG	AAU Asparagine AAC AAA Lysine AAG	AGU Serine AGC AGA Arginine AGG	U C A G
G	GUU GUC GUA Valine GUG	GCU GCC GCA Alanine GCG	GAU Aspartic acid GAC GAA Glutamic acid GAG	GGU GGC GGA Glycine GGG	U C A G

tRNA

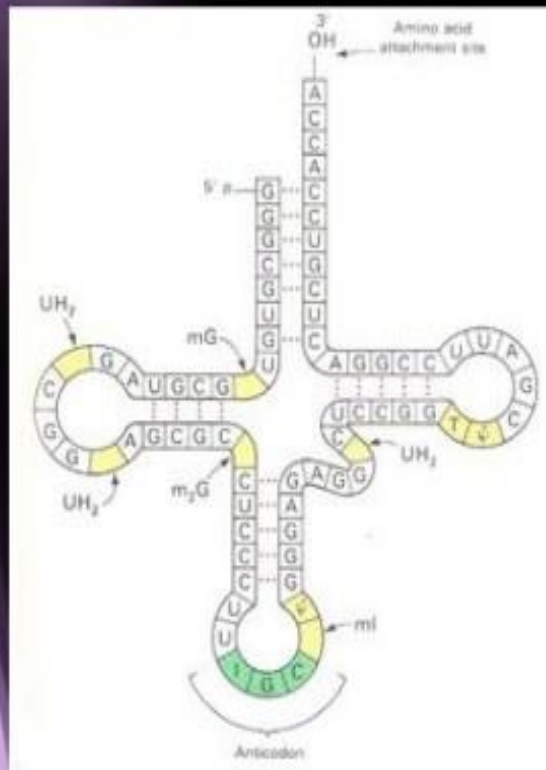


Fig. Base sequence of yeast alanyl tRNA

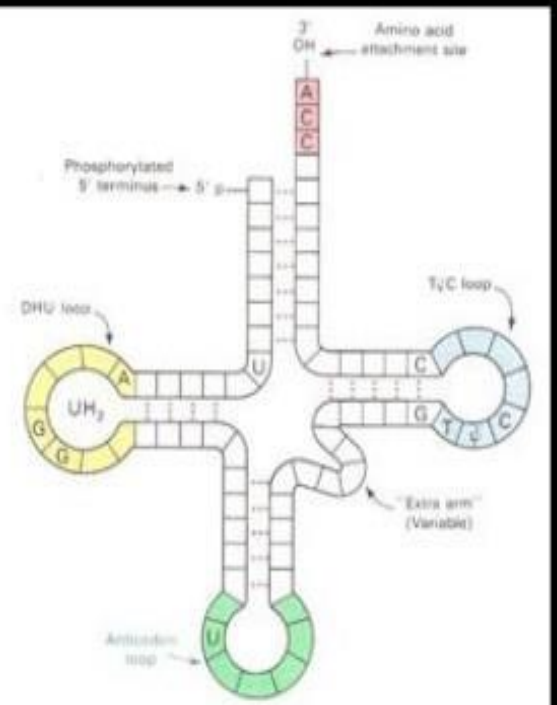


Fig. Common features of tRNA molecule

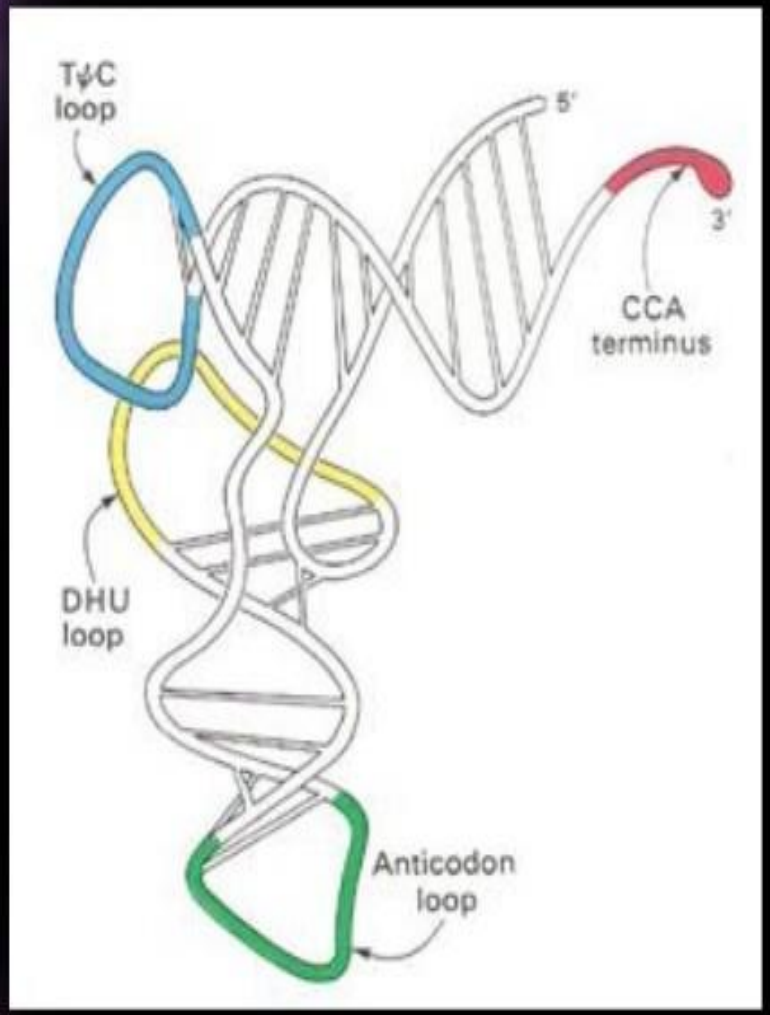


Fig. 3D structure of tRNA

Ribosomes

- Bacterial ribosomes consists of two subunits of unequal size, the larger having a sedimentation coefficient of 50S and the smaller of 30S.

- The two ribosomal subunits have irregular shapes which fit together in such a way that a cleft is formed through which mRNA passes as the ribosome moves along it during the translation process and from which the newly formed polypeptide chain emerges.

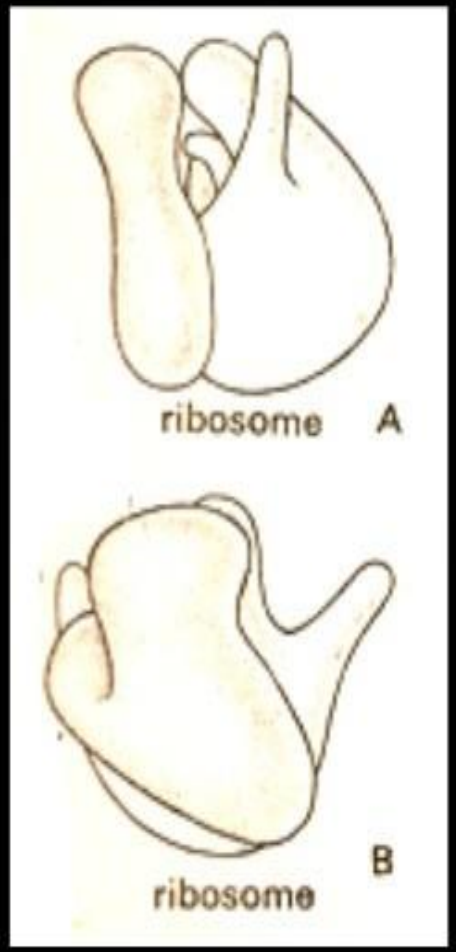


Fig. Ribosomes

Translation

- **Translation** is the first stage of protein biosynthesis (part of the overall process of gene expression).

- Translation is the production of proteins by decoding mRNA produced in transcription.

- It occurs in the cytoplasm where the ribosomes are located.

- Ribosomes are made of a small and large subunit which surrounds the mRNA.

- In translation, messenger RNA (mRNA) is decoded to produce a specific polypeptide according to the rules specified by the genetic code.

- This uses an mRNA sequence as a template to guide the synthesis of a chain of amino acid that form a protein.

- Many types of transcribed RNA, such as transfer RNA, ribosomal RNA, and small nuclear RNA are not necessarily translated into an amino acid sequence.

- **Translation** proceeds in four phases:
  - activation,
  - initiation,
  - elongation and
  - termination

  (all describing the growth of the amino acid chain, or polypeptide that is the product of translation).

  Amino acids are brought to ribosomes and assembled into proteins.

Activation

- In activation, the correct amino acid is covalently bonded to the correct transfer RNA (tRNA).
- While this is not technically a step in translation, it is required for translation to proceed.
- The amino acid is joined by its carboxyl group to the 3' OH of the tRNA by an ester bond.
- When the tRNA has an amino acid linked to it, it is termed "charged".

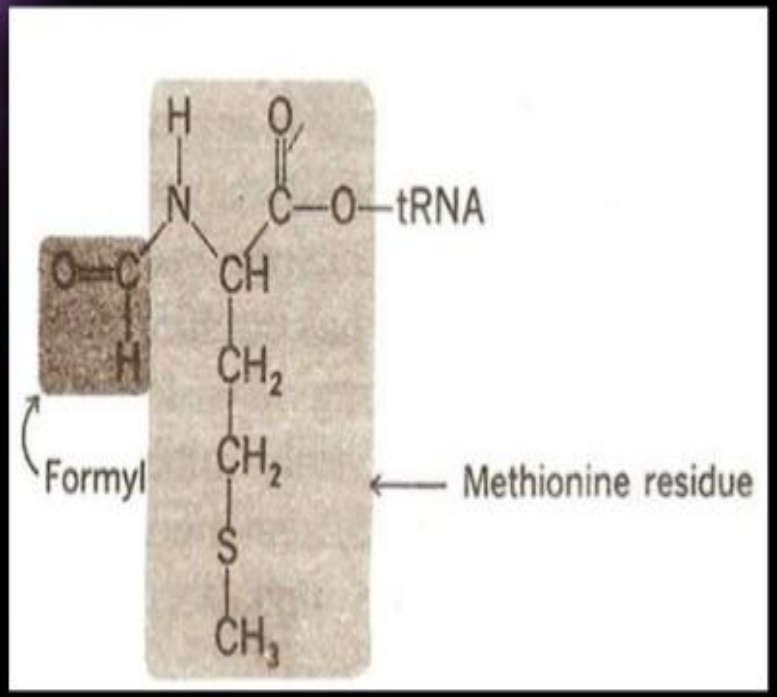


Fig. Charged tRNA (N-formyl methionyl $tRNA_f^{met}$)

In Prokaryotes initiation requires the large and small ribosome subunits, the mRNA, the initiator tRNA and three initiation factors (IF1, IF2, IF3) and GTP. The overall sequence of the event is as follows

- IF3 bind to the free 30S subunit, this helps to prevent the large subunit binding to it without an mRNA molecule and forming an inactive ribosome

- IF2 complexed with GTP and IF1 then binds to the small subunit. It will assist the charged initiator tRNA to bind.

- The 30S subunit attached to an mRNA molecule making use of the ribosome binding site (RBS) on the mRNA

- The initiator tRNA can then bind to the complex by base pairing of its anticodon with the AUG codon on mRNA.

- At this point, IF3 can be released, as its role in keeping the subunits apart and helping the mRNA to bind are complete.

- This complex is called 30S initiation complex

- The 50S subunit can now bind, which displace IF1 and IF2, and the GTP is hydrolysed in this energy consuming step.

- This complex is called as 70S initiation complex.

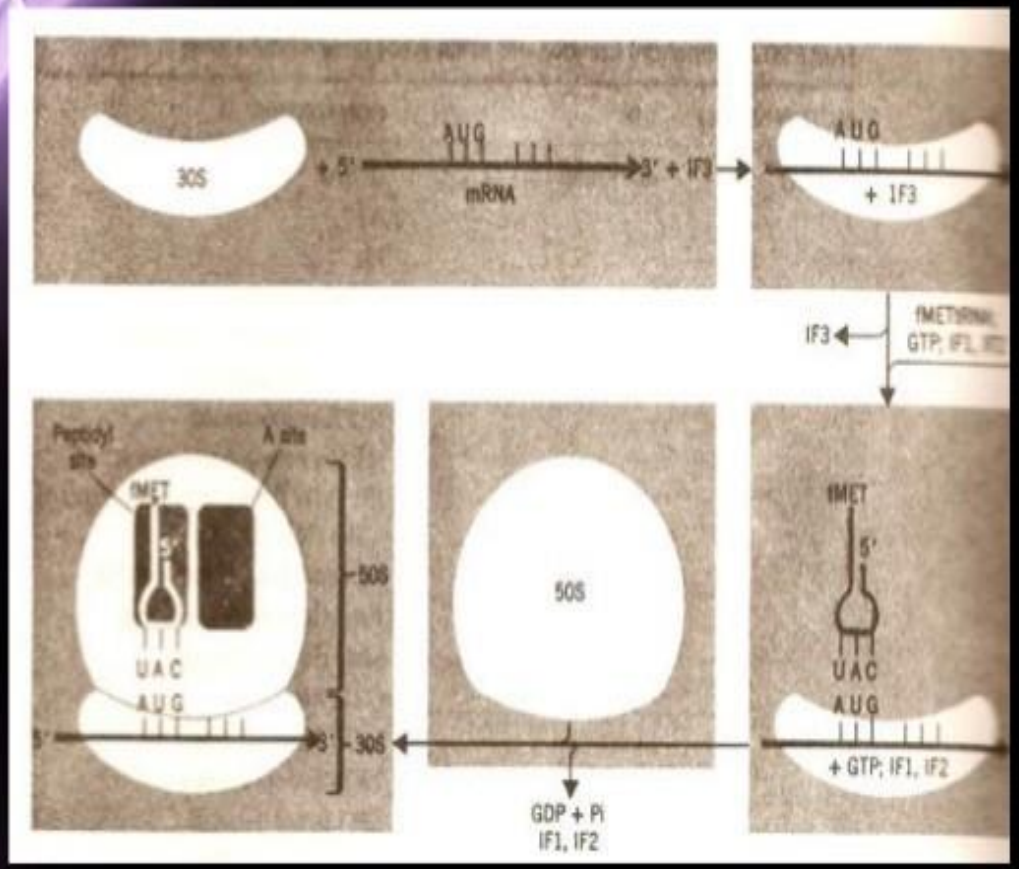


Fig. Formation of the 70S initiation complex

- The assembled ribosome has two tRNA binding sites.
- These are called the A and P sites, for amino acyl and peptidyl sites.
- The A site is where incoming amino acyl tRNA molecules bind, and the P site is where the growing polypeptide chain is usually found.
- These sites are in the cleft of small subunit and contain adjacent codons that are being translated.

- One major outcome of initiation is the placement of the initiator tRNA in the P site.
- It is the only tRNA that does this, as all other must enter the A site.

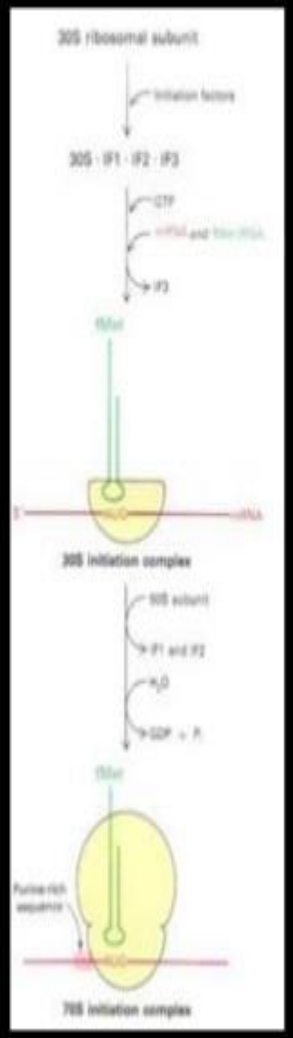


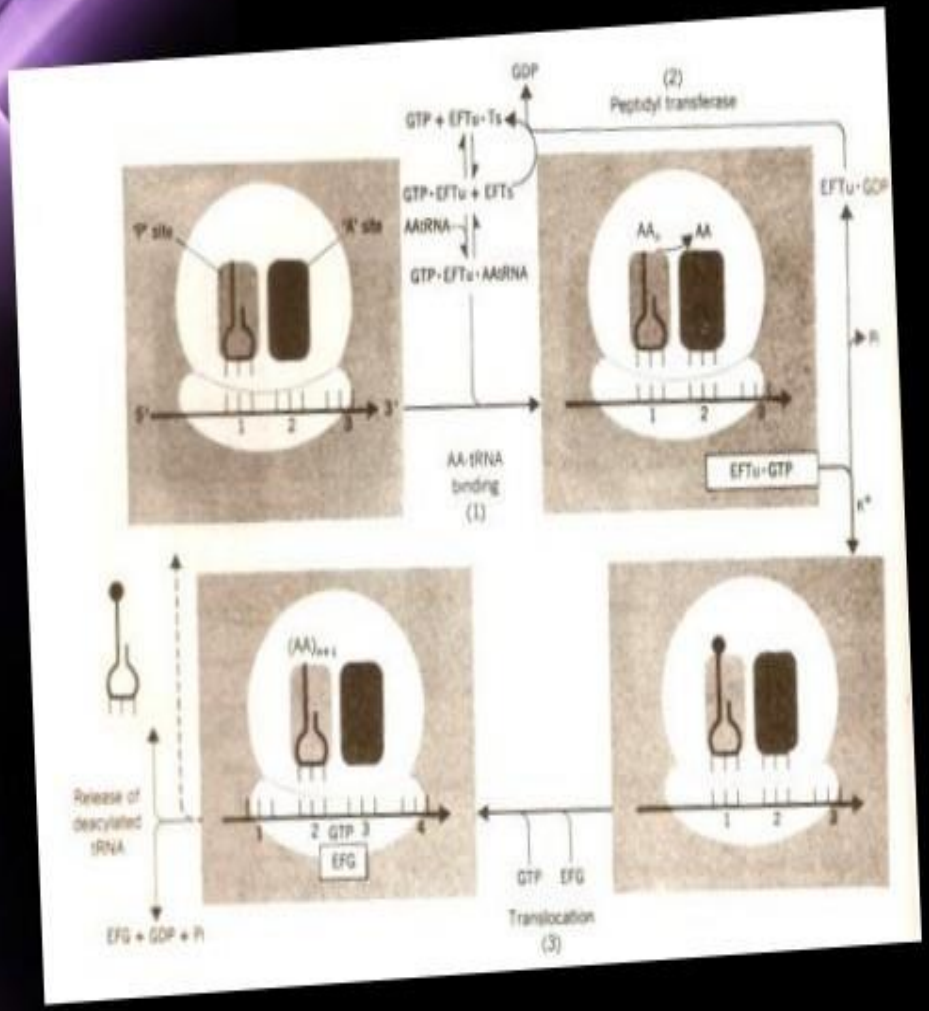
Fig. Initiation phase of protein synthesis

- With the formation of **70S initiation complex** the elongation cycle can begin.
- In involves three elongation factors **EF-Tu**, **EF-Ts** and **EF-G**, GTP, charged tRNA and the 70S initiation complex.

Elongation is divided into three steps:

1. Amino acyl tRNA delivery.

- EF-Tu is required to deliver the amino acyl tRNA to the A site and energy is consumed in this step by the hydrolysis of GTP.
- The released EF-Tu. GDP complex is regenerated with the help of EF-Ts.
- In the EF-Tu EF-Ts exchange cycle EF-Ts displaces the GDP and subsequently is displaced itself by GTP.
- The resultant EF-Tu.GTP complex is now able to bind another amino acyl tRNA and deliver it to the ribosome.
- All amino acyl tRNAs can form this complex with EF-Tu except the initiator tRNA.

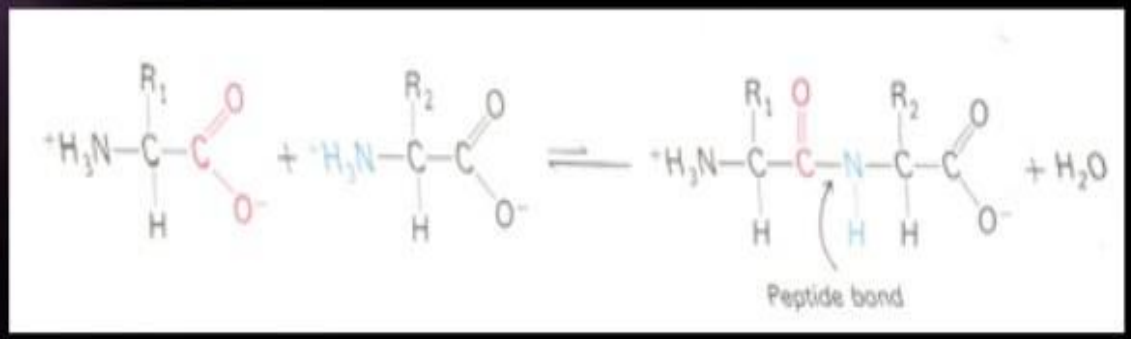


- Fig. Elongation of polypeptide chain

2. Peptide bond formation.

- After aminoacyl-tRNA delivery, the A- and P- sites are both occupied and the two amino acids that are to be joined are in close proximity.

- The peptidyl transferase activity of the 50S subunit can now form a peptide bond between these two amino acids without the input of any more energy, since energy in the form of ATP was used to charge the tRNA.



- **Fig.** Peptide bond formation

3. Translocation.

- A complex of EF-G (translocase) and GTP binds to the ribosome and, in an energy consuming step, the discharged tRNA is ejected from the P-site, the peptidyl-tRNA is moved from the A-site to the P-site and the mRNA moves by one codon relative to one codon to the ribosome.

- GDP and EF-G are released, the latter being reusable. A new codon is now present in the vacant A-site.

The cycle is repeated until one of the termination codons (UAA, UAG and UGA) appear in the A-site.

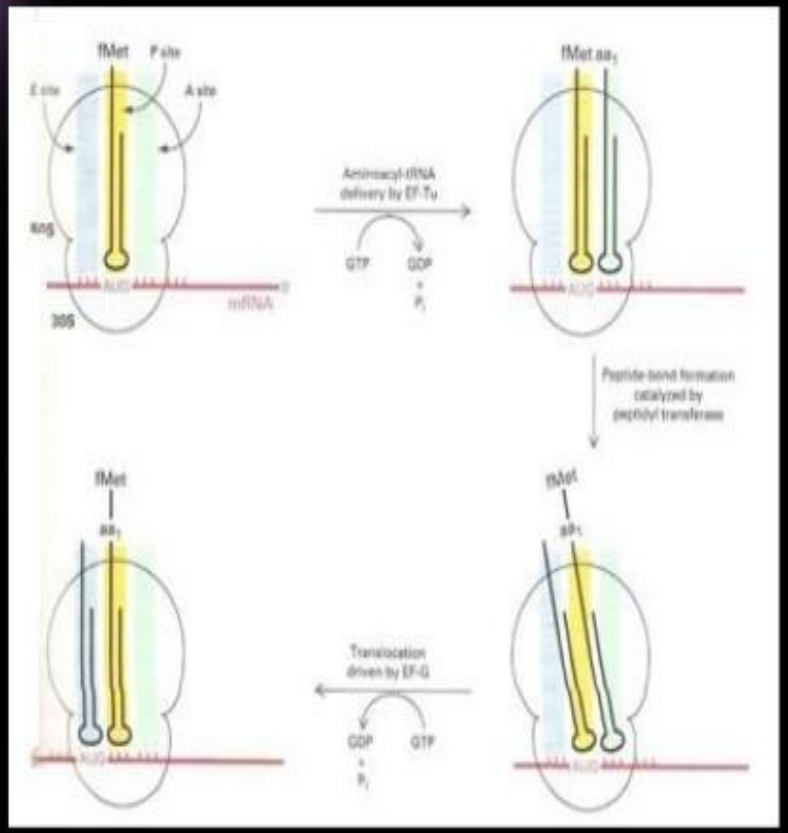


Fig. Translocation

- Termination of the polypeptide happens when the A site of the ribosome faces a stop codon (UAA, UAG, or UGA).

- When this happens, no tRNA can recognize it, but a releasing factor can recognize nonsense codons and causes the release of the polypeptide chain.

- The 5' end of the mRNA gives rise to the protein's N-terminus, and the direction of translation can therefore be stated as N->C.

- Termination of polypeptide synthesis is signalled by one of the three termination codons in the mRNA (UAA, UAG and UGA) immediately following the last amino acid codon.
- In prokaryotes, once a termination codon occupies the ribosomal A-site, three termination or release factors, viz., the protein RF1, RF2 and RF3 contribute to-

➢ The hydrolysis of the terminal peptidyl-tRNA bond.

➢ Release of the free polypeptide and the last uncharged tRNA from the P-site

➢ The dissociation of the 70S ribosome into its 30S and 50S subunits

- RF1 recognizes the termination codon UAG and UAA and RF2 recognize UGA and UAA.

- Either RF1 or RF2 binds at the termination codon and induces peptidyl transferase to transfer the growing peptide chain to a water molecule rather than to another amino acid.

- Function of RF3 is not known.

Polyribosomes

- A single strand of mRNA is translated simultaneously by many ribosomes, spaced closely together.
- Such clusters of ribosomes are called polysomes or polyribosomes.
- The simultaneous translation of a single mRNA by many ribosomes allow highly efficient use of the mRNA

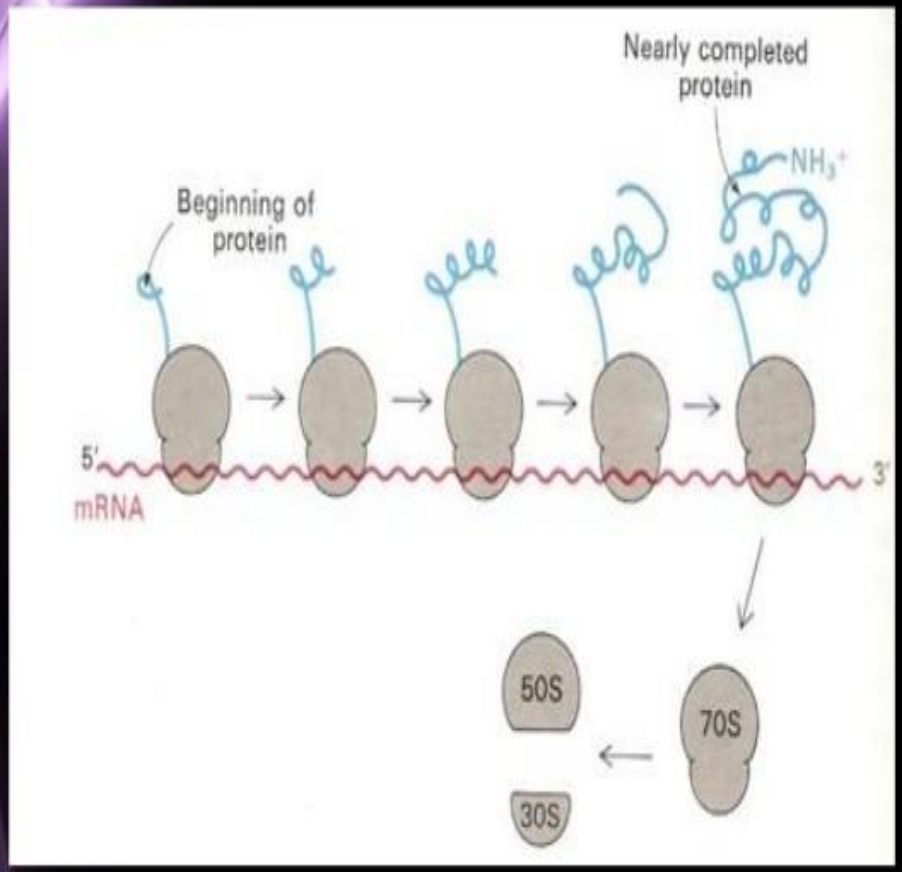
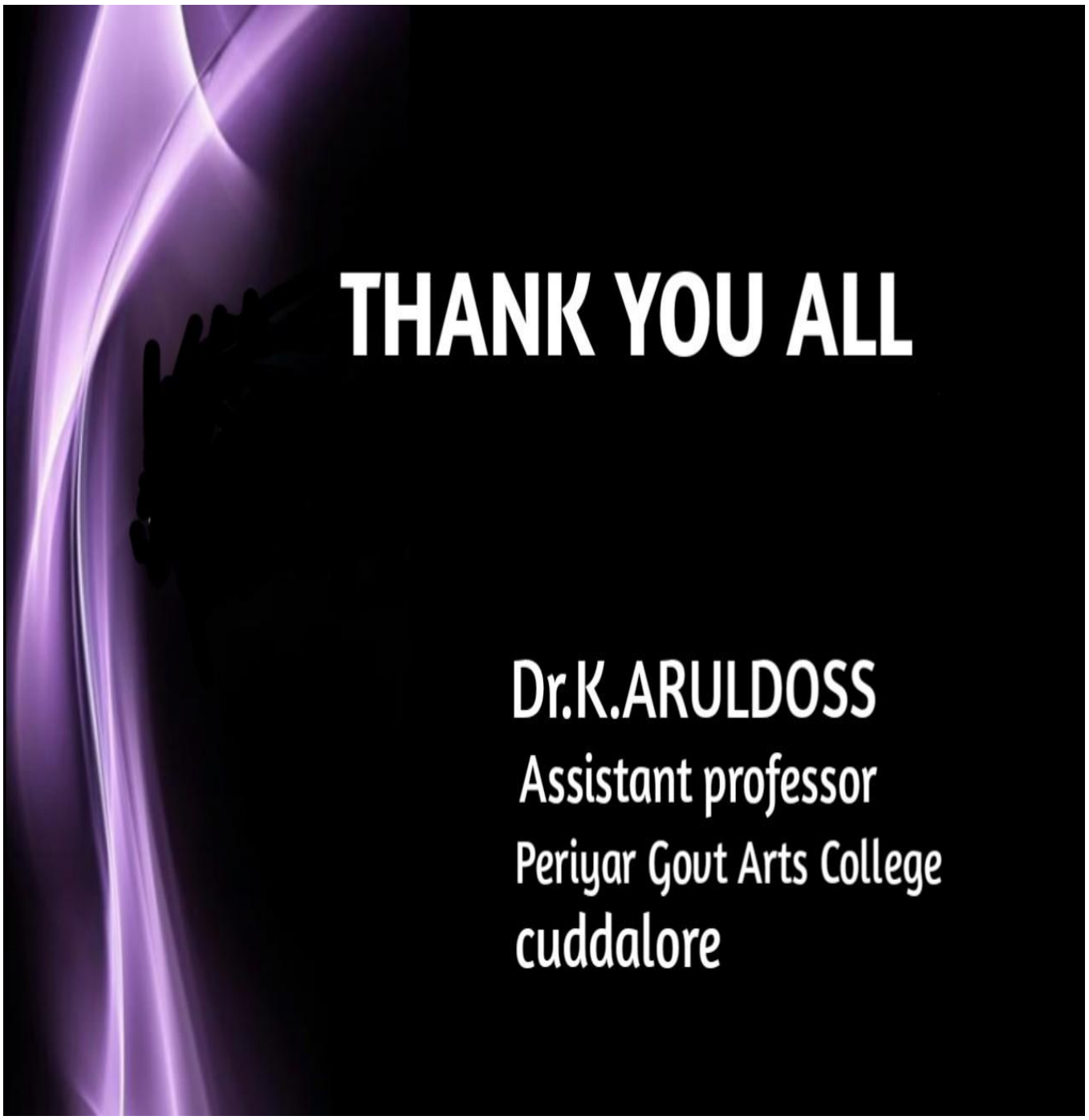


Fig. Polyribosomes



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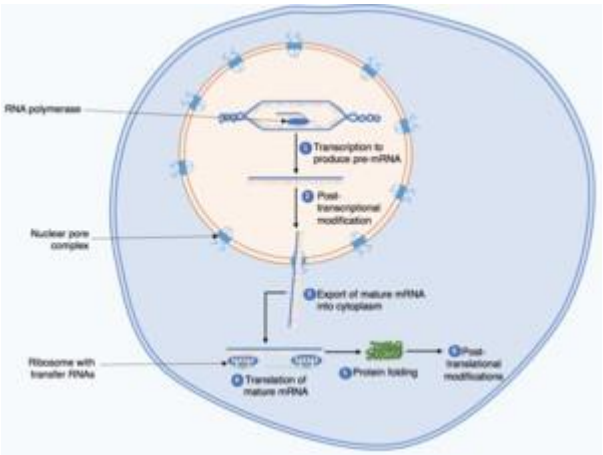
Protein biosynthesis



Protein biosynthesis starting with transcriptionand post-transcriptional modifications in thenucleus.

Then the mature mRNA is exported to the cytoplasm where it is translated. The polypeptide chain then folds and is post-translationallymodified.

Protein biosynthesis (or **protein synthesis**) is a core biological process, occurring inside cells, balancing the loss of cellular proteins (via degradation or export) through the production of new proteins. Proteins perform a variety of critical functions as enzymes, structural proteins or hormones and therefore, are crucial biological components. Protein synthesis is a very similar process for both prokaryotes and eukaryotes but there are some distinct differences.[1]

Protein synthesis can be divided broadly into two phases - transcription and translation. During transcription, a section

of DNA encoding a protein, known as a gene, is converted into a template molecule called messenger RNA. This conversion is carried out by enzymes, known as RNA polymerases, in the nucleus of the cell.[2] In eukaryotes, this messenger RNA (mRNA) is initially produced in a premature form (pre-mRNA) which undergoes post-transcriptional modifications to produce mature mRNA. The mature mRNA is exported from the nucleus via nuclear pores to the cytoplasm of the cell for translation to occur. During translation, the mRNA is read by ribosomes which use the nucleotide sequence of the mRNA to determine the

sequence of amino acids. The ribosomes catalyse the formation of covalent peptide bonds between the encoded amino acids to form a polypeptide chain.

Following translation the polypeptide chain must fold to form a functional protein, for example, to function as an enzyme the polypeptide chain must fold correctly to produce a functional active site. In order to adopt a functional three-dimensional (3D) shape, the polypeptide chain must first form a series of smaller underlying structures called secondary structures. The polypeptide chain in these secondary structures then folds to produce the

overall 3D tertiary structure. Once correctly folded, the protein can undergo further maturation through different post-translational modifications. Post-translational modifications can alter the protein's ability to function, where it is located within the cell (e.g. cytoplasm or nucleus) and the protein's ability to interact with other proteins.[3]

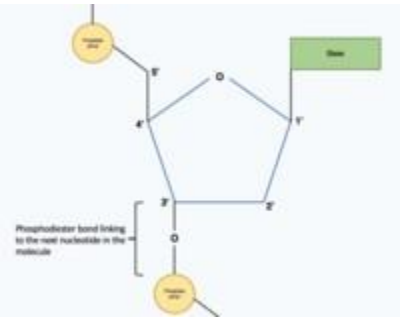
Protein biosynthesis has a key role in disease as changes and errors in this process, through underlying DNA mutations or protein misfolding, are often the underlying causes of a disease. DNA mutations change the subsequent mRNA

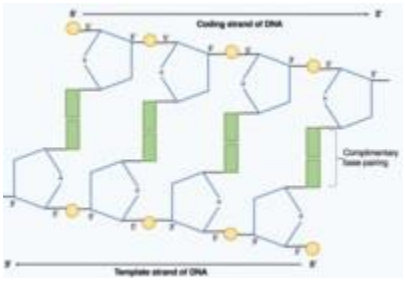
sequence, which then alters the mRNA encoded amino acid sequence. Mutations can cause the polypeptide chain to be shorter by generating a stop sequence which causes early termination of translation. Alternatively, a mutation in the mRNA sequence changes the specific amino acid encoded at that position in the polypeptide chain. This amino acid change can impact the proteins ability to function or to fold correctly.[4] Misfolded proteins are often implicated in disease as improperly folded proteins have a tendency to stick together to form dense protein clumps. These clumps are linked to a range of diseases, often neurological,

including Alzheimer's disease and Parkinson's disease.[5]

Transcription

Transcription occurs in the nucleus using DNA as a template to produce mRNA. In eukaryotes, this mRNA molecule is known as pre-mRNA as it undergoes post-transcriptional modifications in the nucleus to produce a mature mRNA molecule. However, in prokaryotes post-transcriptional modifications are not required so the mature mRNA molecule is immediately produced by transcription.[1]





Illustrate the structure of a nucleotide with the 5 carbons labelled demonstrating the 5' nature of the phosphate group and 3' nature of hydroxyl group needed to form the connective phosphodieste r bonds

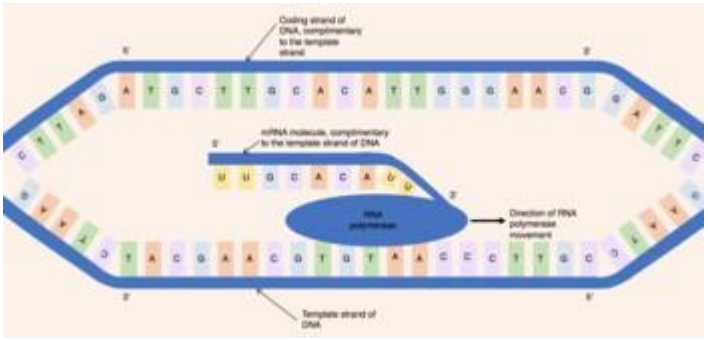
Illustrates the intrinsic directionality of DNA molecule with the coding strand running 5' to 3' and the complimentary template strand running 3' to 5'

Initially, an enzyme known as a helicase acts on the molecule of DNA. DNA has an antiparallel, double helix structure composed of two, complementary polynucleotide strands, held together by hydrogen bonds between the base pairs. The helicase disrupts the hydrogen bonds causing a region of DNA - corresponding to a gene - to unwind, separating the two DNA strands and exposing a series of bases. Despite DNA being a double stranded molecule, only one of the strands acts as a template for pre-mRNA synthesis - this strand is known as the template strand. The other DNA strand (which is

complementary to the template strand) is known as the coding strand.[6]

Both DNA and RNA have intrinsic directionality, meaning there are two distinct ends of the molecule. This property of directionality is due to the asymmetrical underlying nucleotide subunits, with a phosphate group on one side of the pentose sugar and a base on the other. The five carbons in the pentose sugar are numbered from 1' (where ' means prime) to 5'. Therefore, the phosphodiester bonds connecting the nucleotides are formed by joining the hydroxyl group of on the 3' carbon of one

nucleotide to the phosphate group on the 5' carbon of another nucleotide. Hence, the coding strand of DNA runs in a 5' to 3' direction and the complementary, template DNA strand runs in the opposite direction from 3' to 5'.[1]



Illustrates the conversion of the template strand of DNA to the pre-mRNA molecule by RNA polymerase.

The enzyme RNA polymerase binds to the exposed template strand and reads from

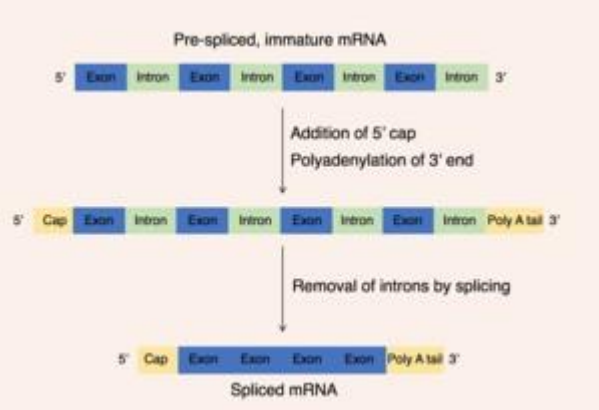
the gene in the 3' to 5' direction. Simultaneously, the RNA polymerase synthesises a single strand of pre-mRNA in the 5'-to-3' direction by catalysing the formation of phosphodiester bonds between activated nucleotides (free in the nucleus) that are capable of complementary base pairing with the template strand. Behind the moving RNA polymerase the two strands of DNA rejoin, so only 12 base pairs of DNA are exposed at one time.[6] RNA polymerase builds the pre-mRNA molecule at a rate of 20 nucleotides per second enabling the production of thousands of pre-mRNA molecules from the same gene in an hour.

Despite the fast rate of synthesis, the RNA polymerase enzyme contains its own proofreading mechanism. The proofreading mechanisms allows the RNA polymerase to remove incorrect nucleotides (which are not complementary to the template strand of DNA) from the growing pre-mRNA molecule through an excision reaction.[1] When RNA polymerases reaches a specific DNA sequence which terminates transcription, RNA polymerase detaches and pre-mRNA synthesis is complete.[6]

The pre-mRNA molecule synthesised is complementary to the template DNA

strand and shares the same nucleotide sequence as the coding DNA strand. However, there is one crucial difference in the nucleotide composition of DNA and mRNA molecules. DNA is composed of the bases - guanine, cytosine, adenine and thymine (G, C, A and T) - RNA is also composed of four bases - guanine, cytosine, adenine and uracil. In RNA molecules, the DNA base thymine is replaced by uracil which is able to base pair with adenine. Therefore, in the pre-mRNA molecule, all complementary bases which would be thymine in the coding DNA strand are replaced by uracil.[7]

Post-transcriptional modifications



Outlines the process of post-transcriptionally modifying pre-mRNA through capping, polyadenylation and splicing to produce a mature mRNA molecule ready for export from the nucleus.

Once transcription is complete, the pre-mRNA molecule undergoes post-transcriptional modifications to produce a mature mRNA molecule.

There are 3 key steps within post-transcriptional modifications:

1. Addition of a 5' cap to the 5' end of the pre-mRNA molecule
2. Addition of a 3' poly(A) tail is added to the 3' end pre-mRNA molecule
3. Removal of introns via RNA splicing

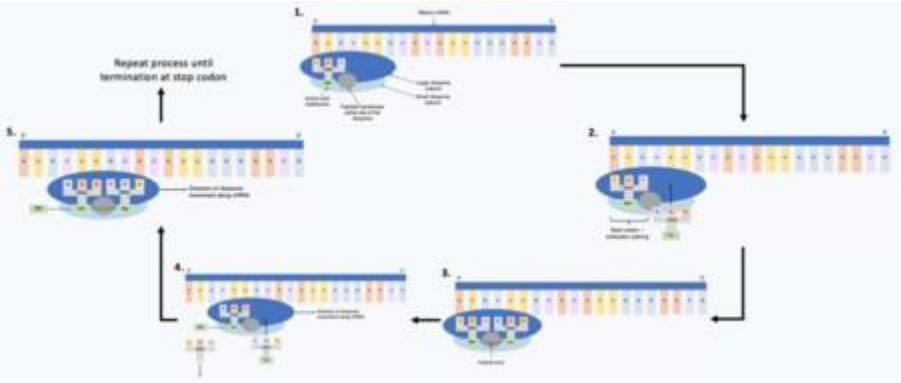
The 5' cap is added to the 5' end of the pre-mRNA molecule and is composed of a guanine nucleotide modified through methylation. The purpose of the 5' cap is to prevent break down of mature mRNA molecules before translation, the cap also aids binding of the ribosome to the mRNA

to start translation [8] and enables mRNA to be differentiated from other RNAs in the cell.[1] In contrast, the 3' Poly(A) tail is added to the 3' end of the mRNA molecule and is composed of 100-200 adenine bases.[8] These distinct mRNA modifications enable the cell to detect that the full mRNA message is intact if both the 5' cap and 3' tail are present.[1]

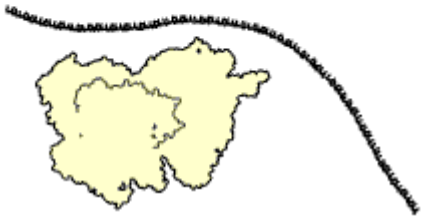
This modified pre-mRNA molecule then undergoes the process of RNA splicing. Genes are composed of a series of introns and exons, introns are nucleotide sequences which do not encode a protein while, exons are nucleotide sequences

that directly encode a protein. Introns and exons are present in both the underlying DNA sequence and the pre-mRNA molecule, therefore, in order to produce a mature mRNA molecule encoding a protein, splicing must occur.[6] During splicing, the intervening introns are removed from the pre-mRNA molecule by a multi-protein complex known as a spliceosome (composed of over 150 proteins and RNA).[9] This mature mRNA molecule is then exported into the cytoplasm through nuclear pores in the envelope of the nucleus.

Translation



Illustrates the translation process showing the cycle of tRNA codon-anti-codon pairing and amino acid incorporation into the growing polypeptide chain by the ribosome.



Demonstrates the action of the ribosome as a biological machine which functions on a nanoscale

to perform translation. The ribosome moves along the mature mRNA molecule incorporating tRNA and producing a polypeptide chain.

During translation, ribosomes synthesise polypeptide chains from mRNA template molecules. In eukaryotes, translation occurs in the cytoplasm of the cell, where the ribosomes are located either free floating or attached to the endoplasmic reticulum. In prokaryotes, which lack a nucleus, the processes of both transcription and translation occur in the cytoplasm.[10]

Ribosomes are complex molecular machines, made of a mixture of protein

and ribosomal RNA, arranged into two subunits (a large and a small subunit), which surround the mRNA molecule. The ribosome reads the mRNA molecule in a 5'-3' direction and uses it as a template to determine the order of amino acids in the polypeptide chain.[11] In order to translate the mRNA molecule, the ribosome uses small molecules, known as transfer RNAs (tRNA), to deliver the correct amino acids to the ribosome. Each tRNA is composed of 70-80 nucleotides and adopts a characteristic cloverleaf structure due to the formation of hydrogen bonds between the nucleotides within the molecule. There are around 60 different types of tRNAs,

each tRNA binds to a specific sequence of three nucleotides (known as a codon) within the mRNA molecule and delivers a specific amino acid.[12]

The ribosome initially attaches to the mRNA at the start codon (AUG) and begins to translate the molecule. The mRNA nucleotide sequence is read in triplets - three adjacent nucleotides in the mRNA molecule correspond to a single codon. Each tRNA has an exposed sequence of three nucleotides, known as the anticodon, which are complementary in sequence to a specific codon that may be present in mRNA. For example, the first

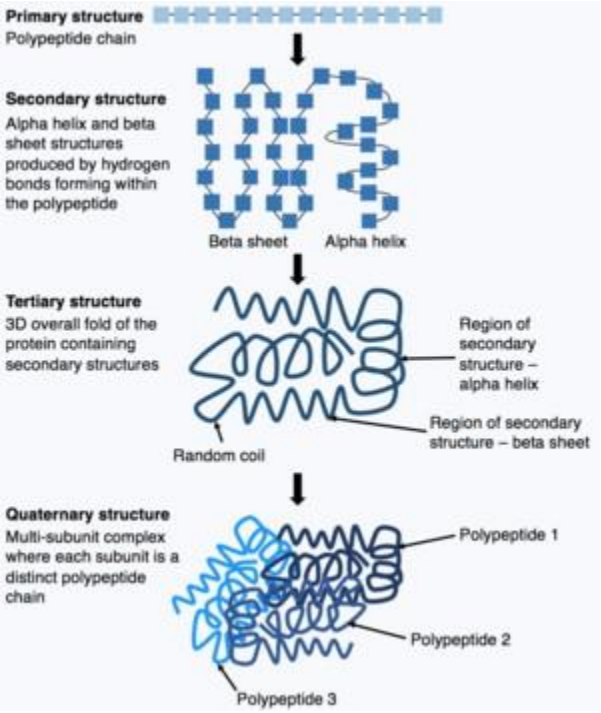
codon encountered is the start codon composed of the nucleotides AUG. The correct tRNA with the anticodon (complementary 3 nucleotide sequence UAC) binds to the mRNA using the ribosome. This tRNA delivers the correct amino acid corresponding to the mRNA codon, in the case of the start codon, this is the amino acid methionine. The next codon (adjacent to the start codon) is then bound by the correct tRNA with complementary anticodon, delivering the next amino acid to ribosome. The ribosome then uses its peptidyl transferase enzymatic activity to catalyse

the formation of the covalent peptide bond between the two adjacent amino acids.[6]

The ribosome then moves along the mRNA molecule to the third codon. The ribosome then releases the first tRNA molecule, as only two tRNA molecules can be brought together by a single ribosome at one time. The next complementary tRNA with the correct anticodon complementary to the third codon is selected, delivering the next amino acid to the ribosome which is covalently joined to the growing polypeptide chain. This process continues with the ribosome moving along the mRNA molecule adding

up to 15 amino acids per second to the polypeptide chain. Behind the first ribosome, up to 50 additional ribosomes can bind to the mRNA molecule forming a polysome, this enables simultaneous synthesis of multiple identical polypeptide chains.[6] Termination of the growing polypeptide chain occurs when the ribosome encounters a stop codon (UAA, UAG, or UGA) in the mRNA molecule. When this occurs, no tRNA can recognise it and a release factor induces the release of the complete polypeptide chain from the ribosome.[12]

Protein folding



Shows the process of a polypeptide chain folding from its initial primary structure through to the quaternary structure.

Once synthesis of the polypeptide chain is complete, the polypeptide chain folds to adopt a specific structure which enables the protein to carry out its functions. The basic form of protein structure is known

as the primary structure, which is simply the polypeptide chain i.e. a sequence of covalently bonded amino acids. The primary structure of a protein is encoded by a gene. Therefore, any changes to the sequence of the gene can alter the primary structure of the protein and all subsequent levels of protein structure, ultimately changing the overall structure and function.

The primary structure of a protein (the polypeptide chain) can then fold or coil to form the secondary structure of the protein. The most common types of secondary structure are known as an

alpha helix or beta sheet, these are small structures produced by hydrogen bonds forming within the polypeptide chain. This secondary structure then folds to produce the tertiary structure of the protein. The tertiary structure is the proteins overall 3D structure which is made of different secondary structures folding together. In the tertiary structure, key protein features e.g. the active site, are folded and formed enabling the protein to function. Finally, some proteins may adopt a complex quaternary structure. Most proteins are made of a single polypeptide chain, however, some proteins are composed of multiple polypeptide chains (known as

subunits) which fold and interact to form the quaternary structure. Hence, the overall protein is a multi-subunit complex composed of multiple folded, polypeptide chain subunits e.g. haemoglobin.[13]

Post-translational modifications

When protein folding into the mature, functional 3D state is complete, it is not necessarily the end of the protein maturation pathway. A folded protein can still undergo further processing through post-translational modifications. There are over 200 known types of post-translational

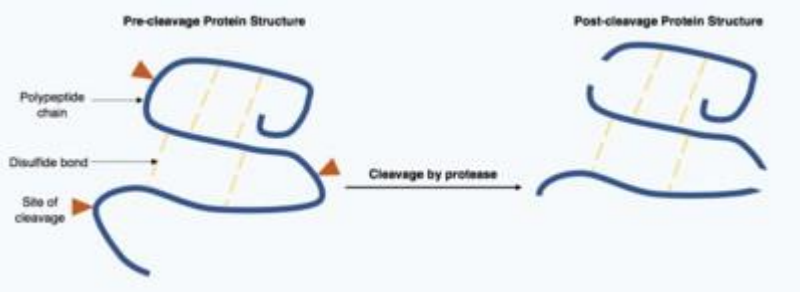
modification, these modifications can alter protein activity, the ability of the protein to interact with other proteins and where the protein is found within the cell e.g. in the cell nucleus or cytoplasm.[14] Through post-translational modifications, the diversity of proteins encoded by the genome is expanded by 2 to 3 orders of magnitude.[15]

There are four key classes of post-translational modification:[16]

1. Cleavage
2. Addition of chemical groups
3. Addition of complex molecules

4. Formation of intramolecular bonds

Cleavage

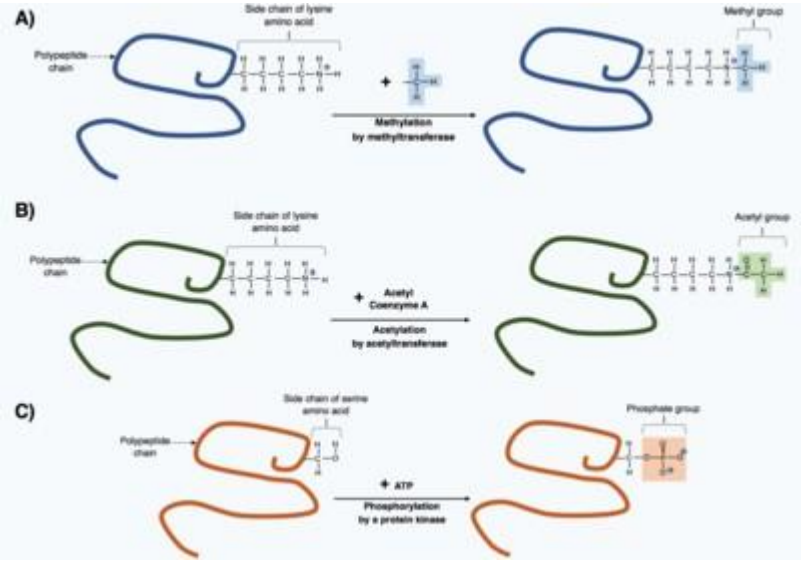


Shows a post-translational modification of the protein by protease cleavage, illustrating that pre-existing bonds are retained even if when the polypeptide chain is cleaved.

Cleavage of proteins is an irreversible post-translational modification carried out by enzymes known as proteases. These proteases are often highly specific and cause hydrolysis of a limited number of

peptide bonds within the target protein. The resulting shortened protein has an altered polypeptide chain with different amino acids at the start and end of the chain. This post-translational modification often alters the proteins function, the protein can be inactivated or activated by the cleavage and can display new biological activities.[17]

Addition of chemical groups



Shows the post-translational modification ofprotein by methylation, acetylation and phosphorylation

Following translation, small chemical groups can be added onto amino acids within the mature protein structure.[18] Examples of processes which add chemical groups to the target protein include methylation, acetylation and phosphorylation.

Methylation is the reversible addition of a methyl group onto an amino acid catalysed by methyltransferase enzymes. Methylation occurs on at least 9 of the 20 common amino acids, however, it mainly occurs on the amino acids lysine and arginine. One example of a protein which is commonly methylated is a histone. Histones are proteins found in the nucleus of the cell. DNA is tightly wrapped round histones and held in place by other proteins and interactions between negative charges in the DNA and positive charges on the histone. A highly specific pattern of amino acid methylation on the histone proteins is used to determine

which regions of DNA are tightly wound and unable to be transcribed and which regions are loosely wound and able to be transcribed.[19]

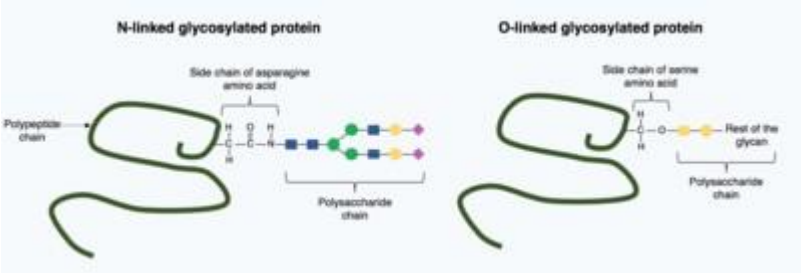
Histone-based regulation of DNA transcription is also modified by acetylation. Acetylation is the reversible covalent addition of an acetyl group onto a lysine amino acid by the enzyme acetyltransferase. The acetyl group is removed from a donor molecule known as acetyl coenzyme A and transferred onto the target protein.[20] Histones undergo acetylation on their lysine residues by enzymes known as histone

acetyltransferase. The effect of acetylation is to weaken the charge interactions between the histone and DNA, thereby making more genes in the DNA accessible for transcription.[21]

The final, prevalent post-translational chemical group modification is phosphorylation. Phosphorylation is the reversible, covalent addition of a phosphate group to specific amino acids (serine, threonine and tyrosine) within the protein. The phosphate group is removed from the donor molecule ATP by a protein kinase and transferred onto the hydroxyl group of the target amino acid, this

produces adenosine diphosphate as a biproduct. This process can be reversed and the phosphate group removed by the enzyme protein phosphatase. Phosphorylation can create a binding site on the phosphorylated protein which enables it to interact with other proteins and generate large, multi-protein complexes. Alternatively, phosphorylation can change the level of protein activity by altering the ability of the protein to bind its substrate.[1]

Addition of complex molecules



Illustrates the difference in structure between N-linked and O-linked glycosylation on a polypeptide chain.

Post-translational modifications can incorporate more complex, large molecules into the folded protein structure. One common example of this is glycosylation, the addition of a polysaccharide molecule, which is widely considered to be most common post-translational modification.[15]

In glycosylation, a polysaccharide molecule (known as a glycan) is covalently added to the target protein by glycosyltransferases enzymes and modified by glycosidases in the endoplasmic reticulum and Golgi apparatus. Glycosylation can have a critical role in determining the final, folded 3D structure of the target protein. In some cases glycosylation is necessary for correct folding. N-linked glycosylation promotes protein folding by increasing solubility and mediates the protein binding to protein chaperones. Chaperones are proteins responsible for folding and

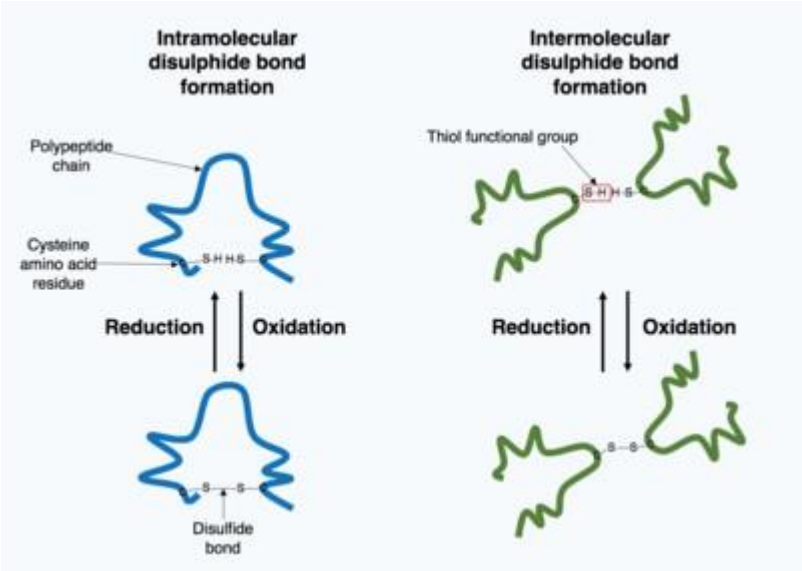
maintaining the structure of other proteins.[1]

There are broadly two types of glycosylation, N-linked glycosylation and O-linked glycosylation. N-linked glycosylation starts in the endoplasmic reticulum with the addition of a precursor glycan. The precursor glycan is modified in the Golgi apparatus to produce complex glycan bound covalently to the nitrogen in an asparagine amino acid. In contrast, O-linked glycosylation is the sequential covalent addition of individual sugars onto the oxygen in the amino acids serine and

threonine within the mature protein structure.[1]

Formation of covalent bonds

E...



Shows the formation of disulphide covalent bonds as a post-translational modification. Disulphide bonds can either form within a single polypeptide chain (left) or between polypeptide chains in a multi- subunit protein complex (right).

Many proteins produced within the cell are secreted outside the cell, therefore, these proteins function as extracellular proteins. Extracellular proteins are exposed to a wide variety of conditions. In order to stabilise the 3D protein structure, covalent bonds are formed either within the protein or between the different polypeptide chains in the quaternary structure. The most prevalent type is a disulfide bond (also known as a disulfide bridge). A disulfide bond is formed between two cysteine amino acids using their side chain chemical groups containing a sulphur atom, these chemical groups are known as thiol functional groups. Disulfide

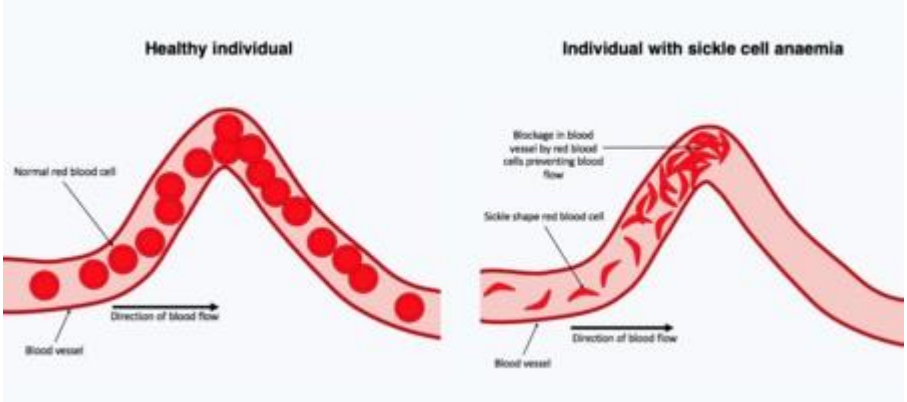
bonds act to stabilise the pre-existing structure of the protein. Disulfide bonds are formed in an oxidation reaction between two thiol groups and therefore, need an oxidising environment to react. As a result, disulfide bonds are typically formed in the oxidising environment of the endoplasmic reticulum catalysed by enzymes called protein disulfide isomerases. Disulfide bonds are rarely formed in the cytoplasm as it is a reducing environment.[1]

Role of protein synthesis in disease

Many diseases are caused by mutations in genes, due to the direct connection between the DNA nucleotide sequence and the amino acid sequence of the encoded protein. Changes to the primary structure of the protein can result in the protein mis-folding or malfunctioning. Mutations within a single gene have been identified as a cause of multiple diseases, including sickle cell disease, known as single gene disorders.

Sickle cell disease

E...



A comparison between a healthy individual and a sufferer of sickle cell anaemia illustrating the different red blood cell shapes and differing blood flow within blood vessels.

Sickle cell disease is a group of diseases caused by a mutation in a subunit of haemoglobin, a protein found in red blood cells responsible for transporting oxygen. The most dangerous of the sickle cell diseases is known as sickle cell anaemia.

Sickle cell anaemia is the most common homozygous recessive single gene disorder, meaning the sufferer must carry a mutation in both copies of the affected gene (one inherited from each parent) to suffer from the disease. Haemoglobin has a complex quaternary structure and is composed of four polypeptide subunits - two A subunits and two B subunits.[22] Patients suffering from sickle cell anaemia have a missense or substitution mutation in the gene encoding the haemoglobin B subunit polypeptide chain. A missense mutation means the nucleotide mutation alters the overall codon triplet such that a different amino acid is paired with the new

codon. In the case of sickle cell anaemia, the most common missense mutation is a single nucleotide mutation from thymine to adenine in the haemoglobin B subunit gene.[23] This changes codon 6 from encoding the amino acid glutamic acid to encoding valine.[22]

This change in the primary structure of the haemoglobin B subunit polypeptide chain alters the functionality of the haemoglobin multi-subunit complex in low oxygen conditions. When red blood cells unload oxygen into the tissues of the body, the mutated haemoglobin protein starts to stick together to form a semi-solid

structure within the red blood cell. This distorts the shape of the red blood cell, resulting in the characteristic "sickle" shape, and reduces cell flexibility. This rigid, distorted red blood cell can accumulate in blood vessels creating a blockage. The blockage prevents blood flow to tissues and can lead to tissue death which causes great pain to the individual.[24]

See also

- Central dogma of molecular biology
- Genetic code
- Gene expression

- Post-translational modification
- Protein folding

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External links

- A useful video visualising the process of converting DNA to protein via transcription and translation
- Video visualising the process of protein folding from the non-functional primary structure to a mature, folded 3D protein structure with reference to the role of mutations and protein mis-folding in disease
- A more advanced video detailing the different types of post-translational modifications and their chemical structures

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Last edited 1 month ago by Cretes

Genetic Disorders

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Periyar Govt Arts College cuddalore

Brief History

- **First there was Gregor Mendel, a monk who studied inherited characteristics. This was followed by Francis crick and James Watson who unraveled the DNA molecule. This has led us to understanding the human genome sequence**

Gregor Mendel

- **1866**
- **Gregor Mendel published the results of his investigations of the inheritance of "factors" in pea plants.**

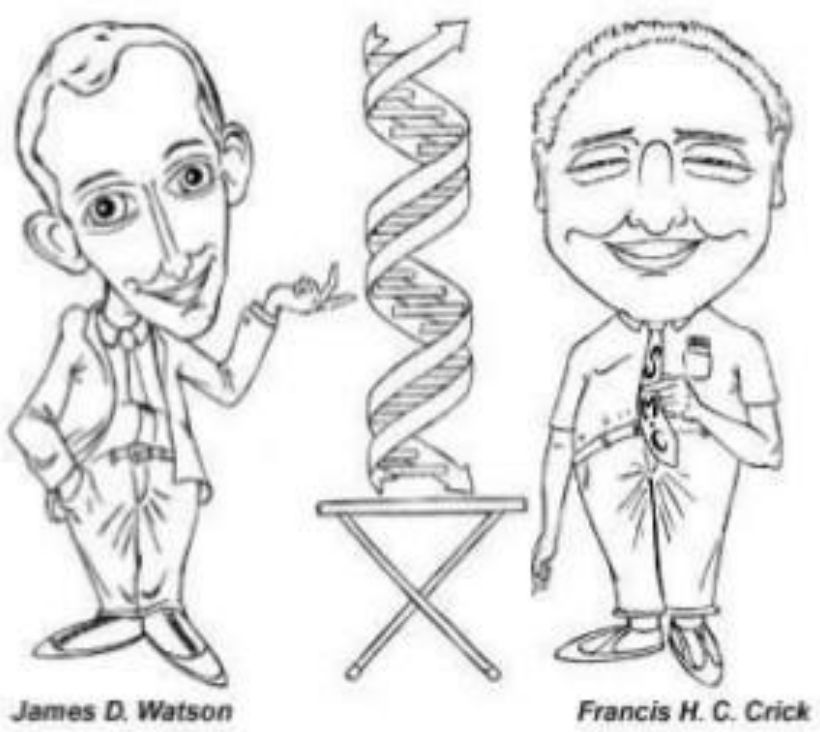
Gregor Mendel

Rosalind Franklin

Rosalind Franklin

- **1950's.**
- **Maurice Wilkins (1916-), Rosalind Franklin (1920-1957), Francis H. C. Crick (1916-) of Britain and James D. Watson (1928-) of the U.S. Discover chemical structure of DNA, starting a new branch of science--molecular biology. .**

Watson and Crick



- **Watson and Crick made a model of the DNA molecule and proved that genes determine heredity**

Arthur Kornberg

Arthur Kornberg

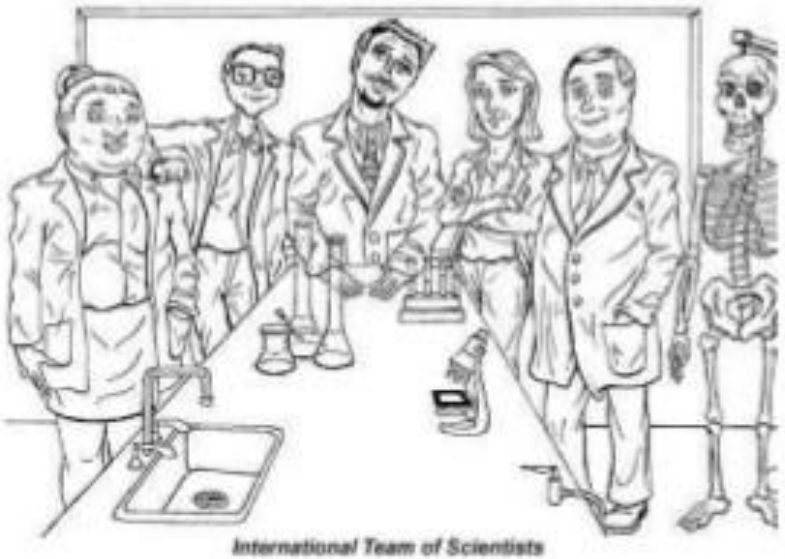
- **1957**
- **Arthur Kornberg (1918-) of the U.S. produced DNA in a test tube.**

Barbara McClintock

Barbara McClintock

- **1983**
- **Barbara McClintock (1902-1992) of the U.S. was awarded the Nobel Prize for her discovery that genes are able to change position on chromosomes.**

DNA Fingerprinting



International Team of Scientists

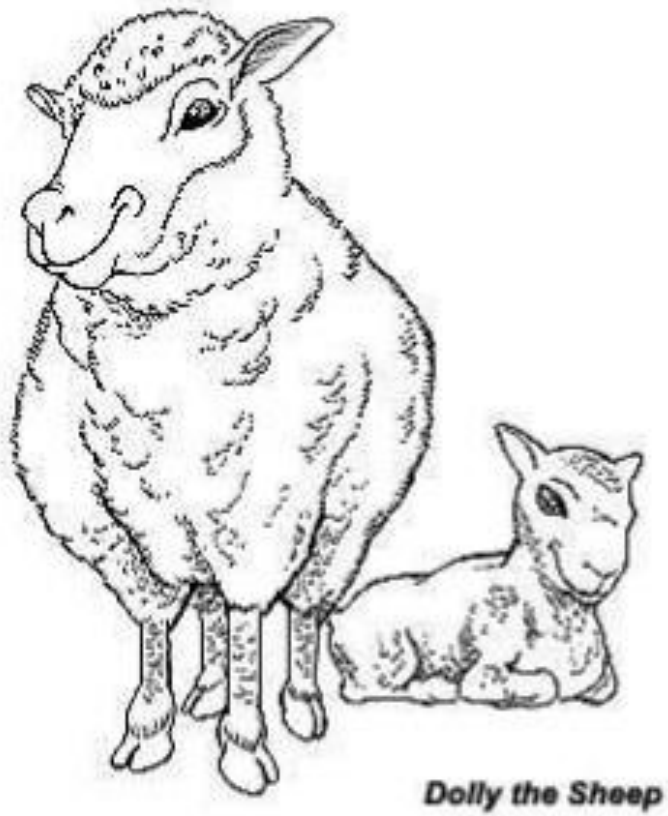
- **The late 1980's.**
- **An international team of scientists began the project to map the human genome.**
- **The first crime conviction based on DNA fingerprinting, in Portland Oregon.**

Gene Therapy

Gene Therapy

- **1990.**
- **Gene therapy was used on patients for the first time.**

Cloning Begins



Dolly the Sheep

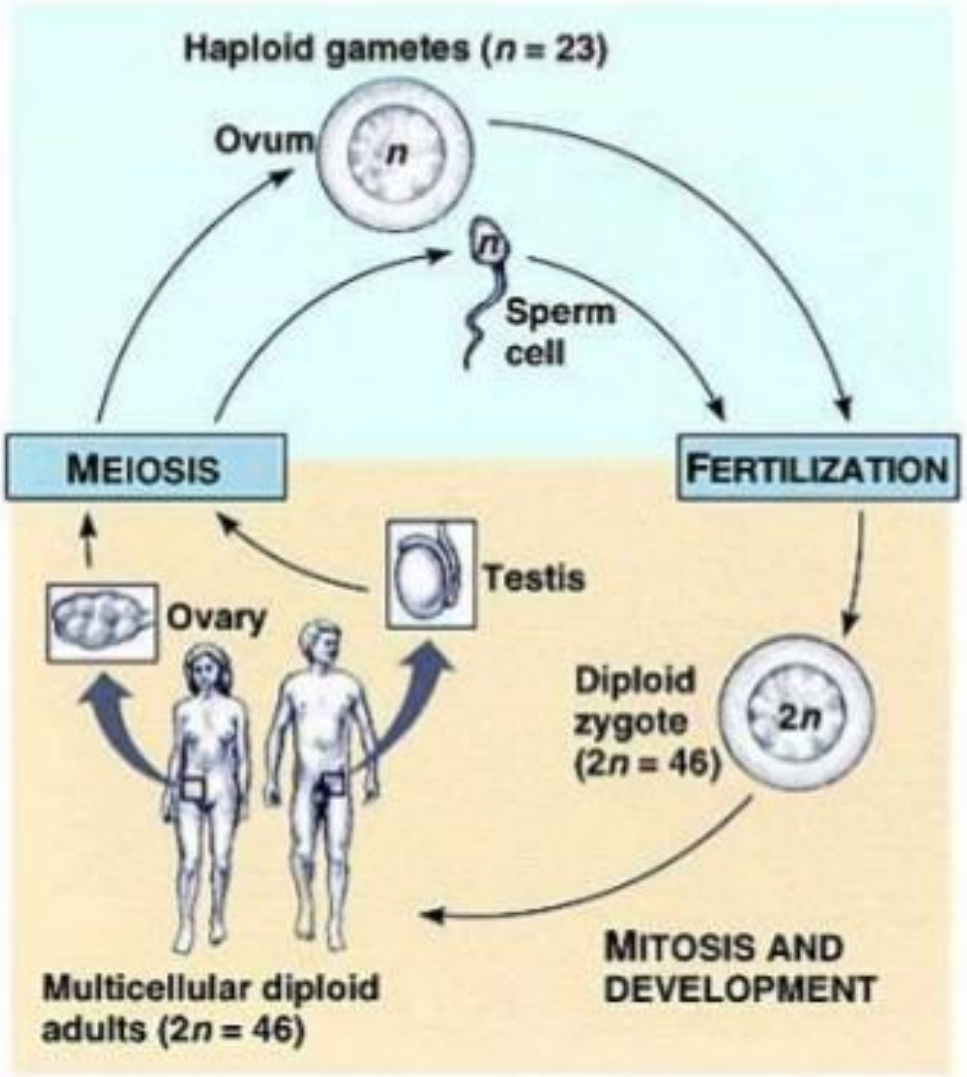
- **1997.**
- **Dolly the sheep - the first adult animal clone.**

Human Genome Project

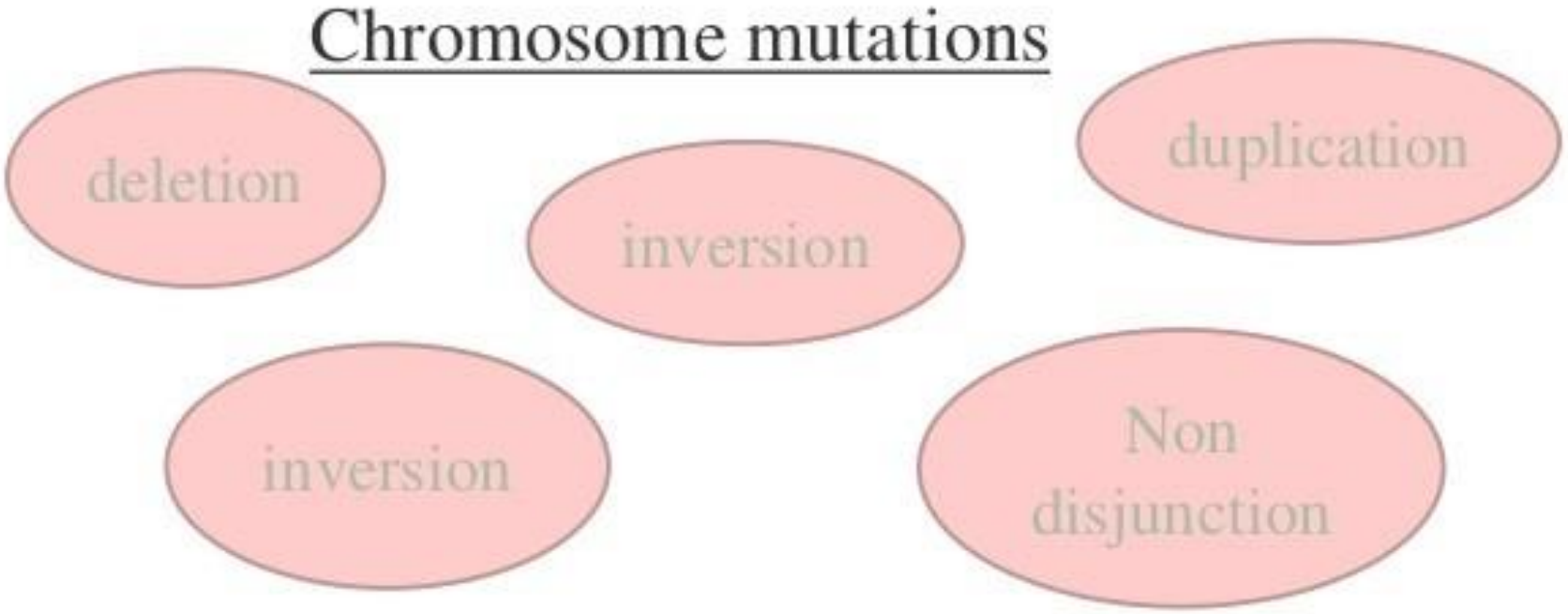
- **.. Imagine a world in which we will be able to treat diseases by altering our very genes, giving us new ones if ours are non-functional, changing bad genes for good ones. For the first time in our existence, we are closer to understanding just what we are. We now have the tools to make the whole world better through science , the science of the human genome.**

Genetic Disorders

Figure 12.3 The human life cycle

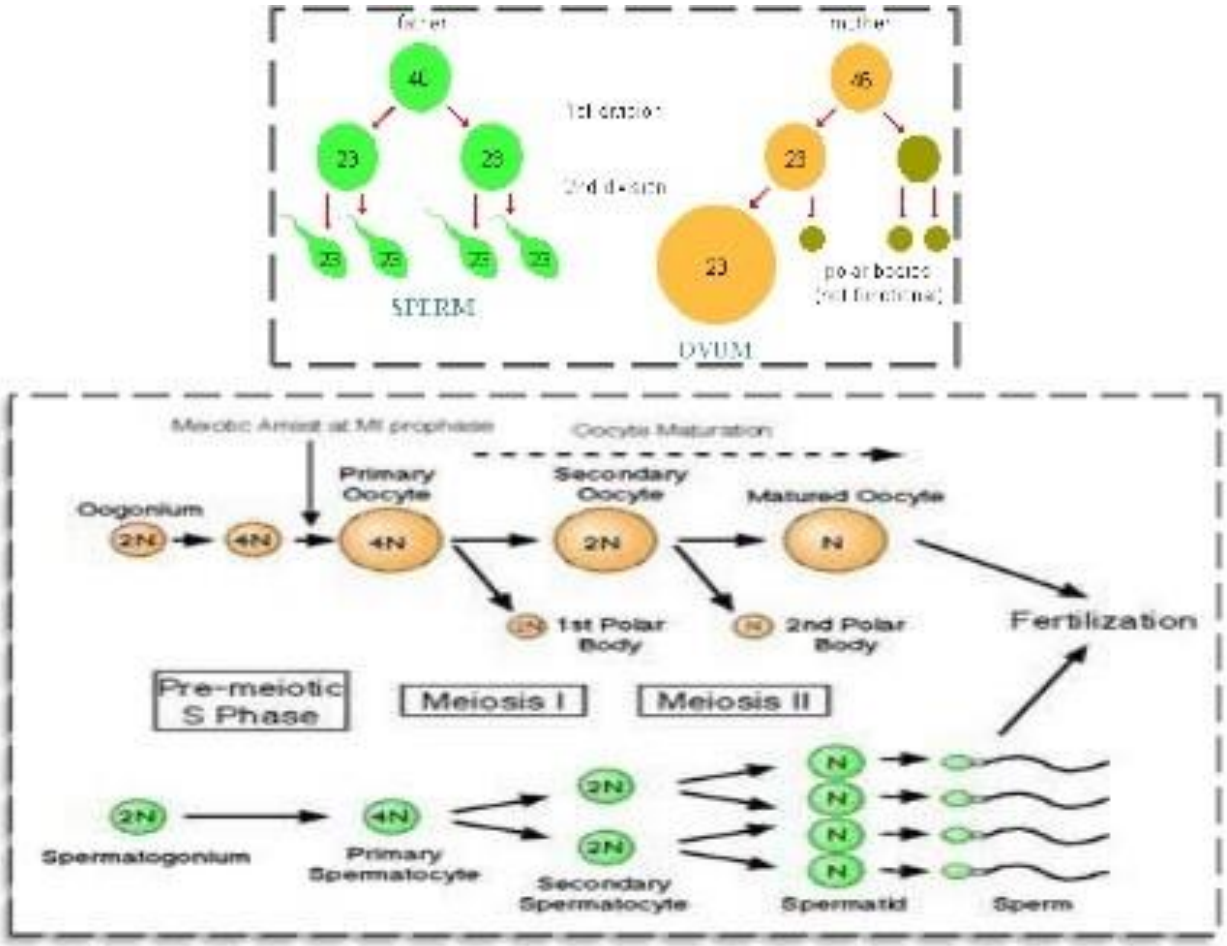


- Chromosomes :
- - sex chromosomes
- - autosomes



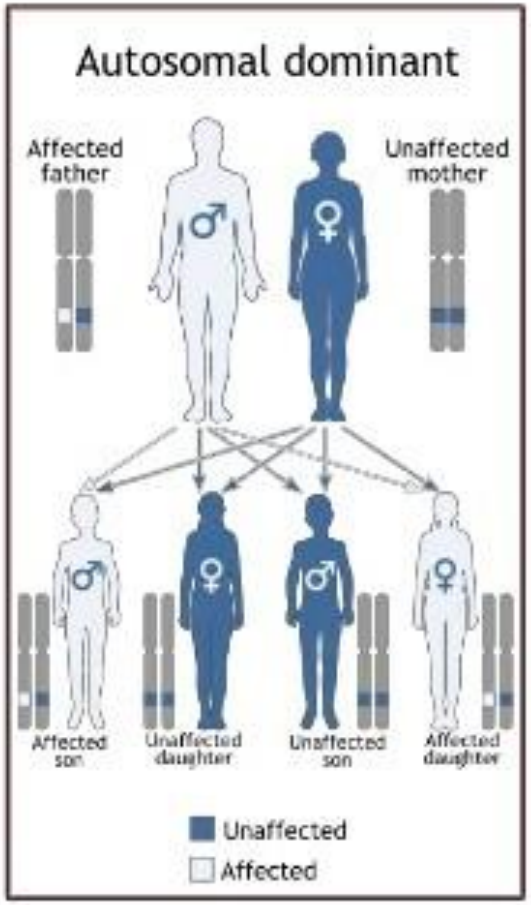
Mutations

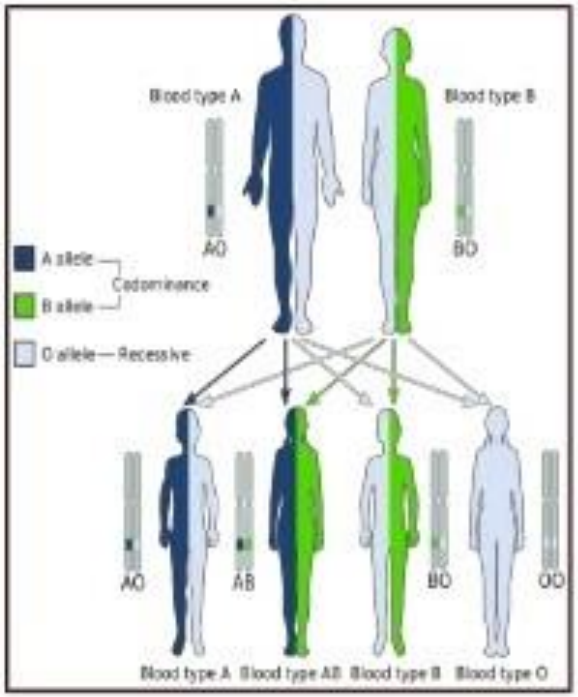
- Gene mutations can be either inherited from a parent or acquired. A hereditary mutation is a mistake that is present in the DNA of virtually all body cells. Hereditary mutations are also called *germ line* mutations because the gene change exists in the reproductive cells and can be passed from generation to generation, from parent to newborn. Moreover, the mutation is copied every time body cells divide

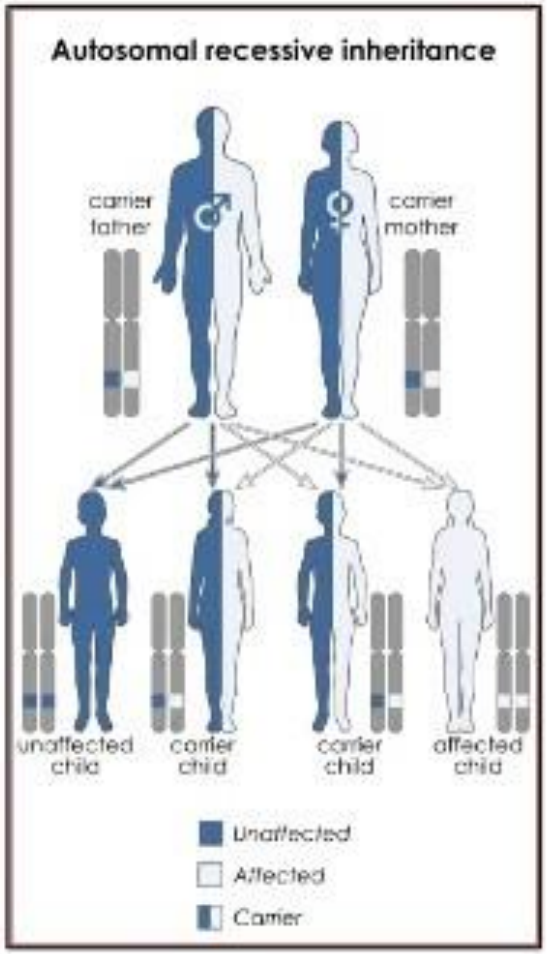

Meiotic Arrest at MI prophase
Oocyte Maturation
Oogonium
Primary Oocyte
Secondary Oocyte
Matured Oocyte
2N
4N
4N
2N
N
1st Polar Body
2nd Polar Body
Fertilization
Pre-meiotic S Phase
Meiosis I
Meiosis II
2N
4N
2N
2N
N
N
N
N
Spermatogonium
Primary Spermatocyte
Secondary Spermatocyte
Spermatid
Sperm

- Mutations occur all the time in every cell in the body. Each cell, however, has the remarkable ability to recognize mistakes and fix them before it passes them along to its descendants. But a cell's DNA repair mechanisms can fail, or be overwhelmed, or become less efficient with age. Over time, mistakes can accumulate.

Dominance


Autosomal dominant
Affected father
Unaffected mother
Affected son
Unaffected daughter
Unaffected son
Affected daughter
Unaffected
Affected

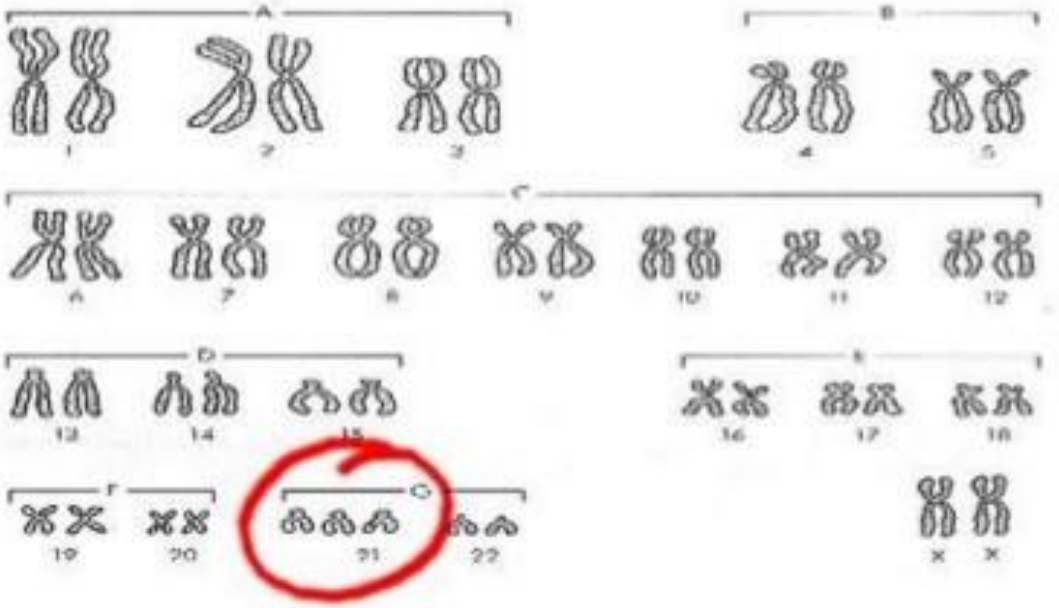

Blood type A
Blood type B
A allele
B allele
Codominance
O allele — Recessive
AO
BO
AO
AB
BO
OO
Blood type A
Blood type AB
Blood type B
Blood type O


Autosomal recessive inheritance
carrier father
carrier mother
unaffected child
carrier child
carrier child
affected child
Unaffected
Affected
Carrier

#1- Down's Syndrome

- Caused by non-disjunction of the 21st chromosome.
- This means that the individual has a trisomy (3 – 2lst chromosomes).

Down's Syndrome or Trisomy 21

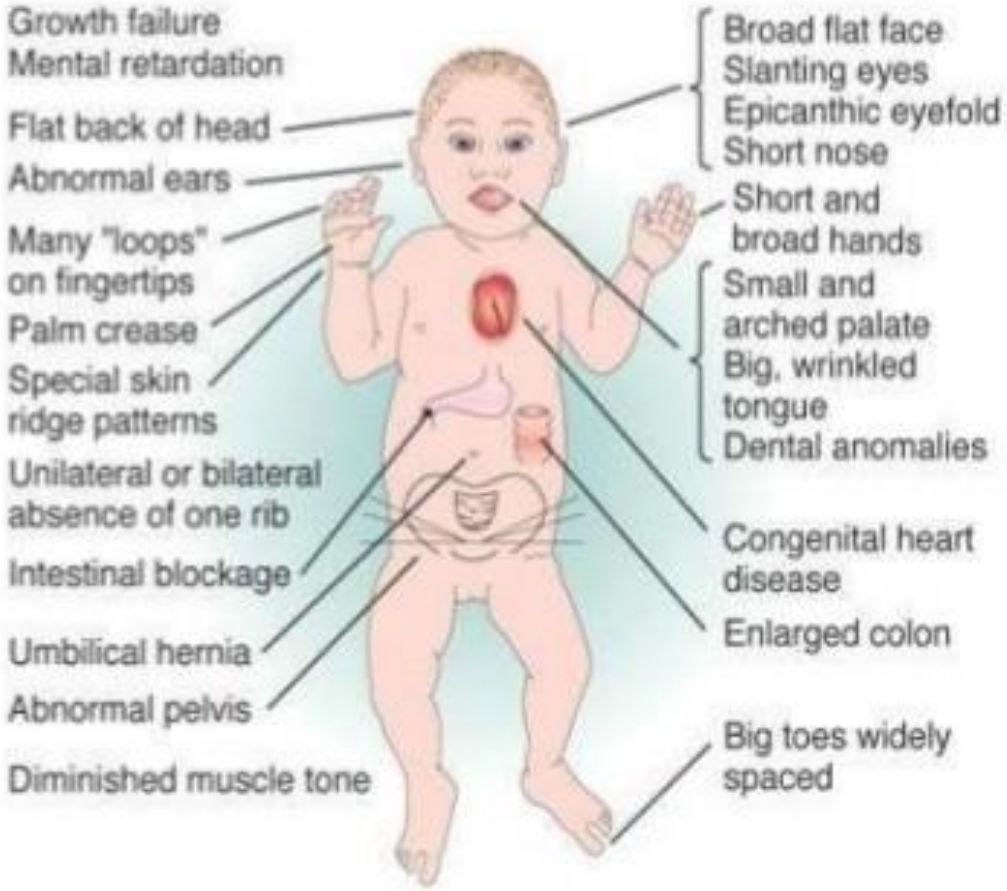


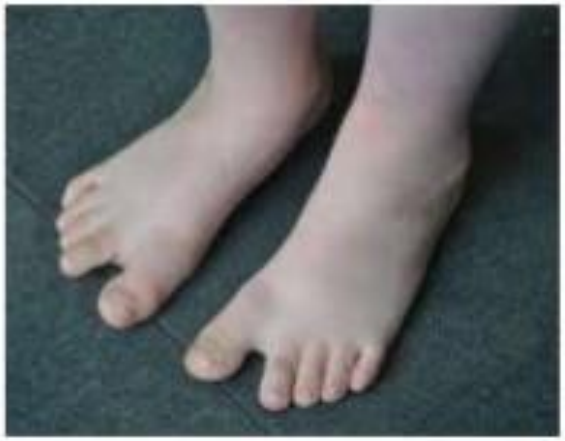
Symptoms of Down Syndrome

- Upward slant to eyes.
- Small ears that fold over at the top.
- Small, flattened nose.
- Small mouth, making tongue appear large.
- Short neck.
- Small hands with short fingers.

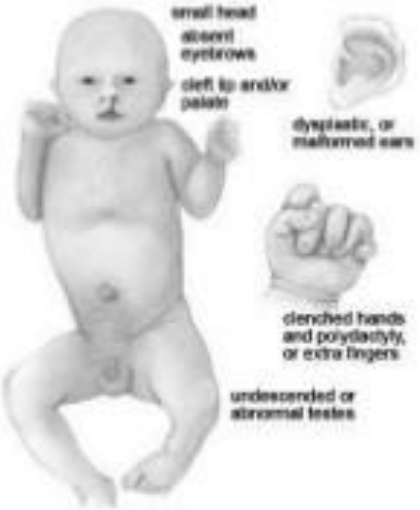
Symptoms of Down Syndrome

- Low muscle tone.
- Single deep crease across center of palm.
- Looseness of joints.
- Small skin folds at the inner corners of the eyes.
- Excessive space between first and second toe.
- In addition, down syndrome always involves some degree of mental retardation, from mild to severe. In most cases, the mental retardation is mild to moderate.


Growth failure
Mental retardation
Flat back of head
Abnormal ears
Many "loops" on fingertips
Palm crease
Special skin ridge patterns
Unilateral or bilateral absence of one rib
Intestinal blockage
Umbilical hernia
Abnormal pelvis
Diminished muscle tone
Broad flat face
Slanting eyes
Epicanthic eyefold
Short nose
Short and broad hands
Small and arched palate
Big, wrinkled tongue
Dental anomalies
Congenital heart disease
Enlarged colon
Big toes widely spaced




Simian crease
Normal palm creases
A.D.A.M.


small head
absent eyebrows
cleft lip and/or palate
dysplastic, or malformed ears
clenched hands and polydactyly, or extra fingers
undescended or abnormal testes

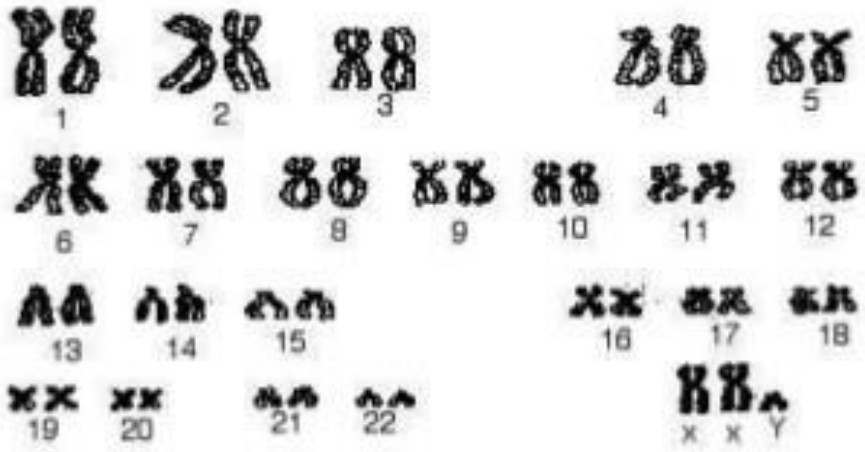
#2 - Kleinfelter's syndrome

(or Klinefleter's)

- Disorder occurring due to nondisjunction of the X chromosome.
- The Sperm containing both X and Y combines with an egg containing the X, results in a male child.
- The egg may contribute the extra X chromosome.

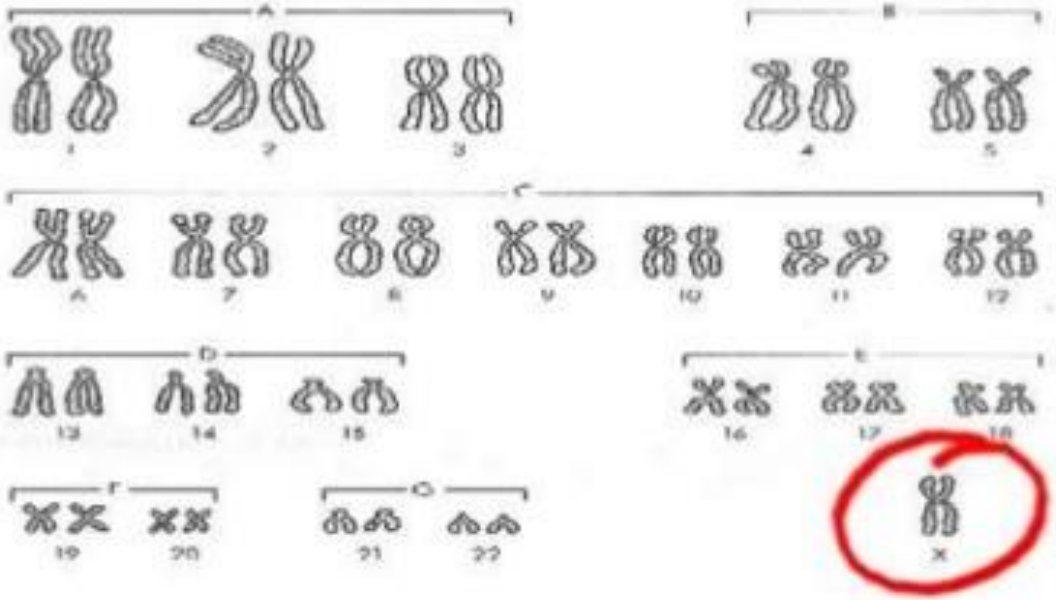
XXY

- **Males with some development of breast tissue normally seen in females.**
- **Little body hair is present, and such person are typically tall, have small testes.**
- **Infertility results from absent sperm.**
- **Evidence of mental retardation may or may not be present.**


1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
X X Y

- Treatment with testosterone has to start at puberty , around the age of 12 years,
- increasing levels of testosterone by therapy is maintaining normal levels of estradiol, FSH and LH

Turner's Syndrome

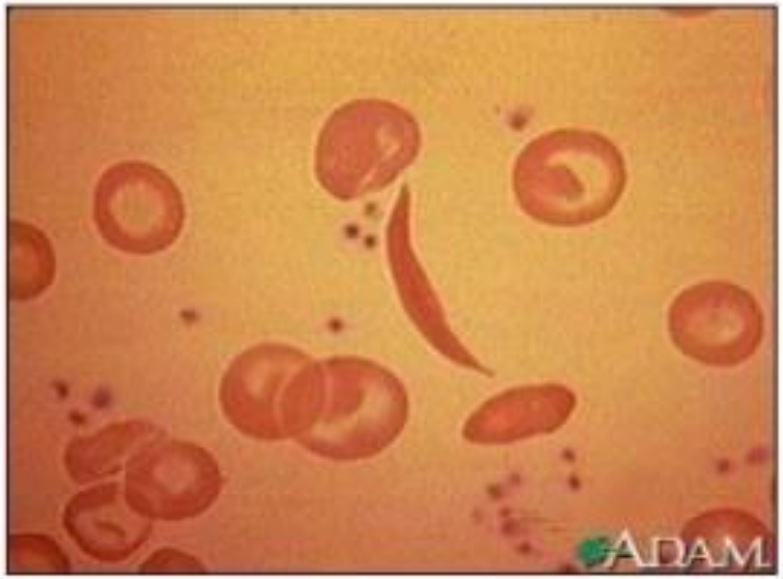


Deletion or partial deletion of X chromosome

ttt :

- **Growth hormone.** Growth hormone therapy is recommended for most girls with Turner syndrome . Growth hormone treatment is usually given several times a week as injections of **Somatropin** (Humatrope, Genotropin, Saizen, others
- **Estrogen therapy.** Most girls with Turner syndrome need to start estrogen and related hormone therapy in order to begin puberty and achieve adult sexual development

#4 - Sickle Cell Anemia

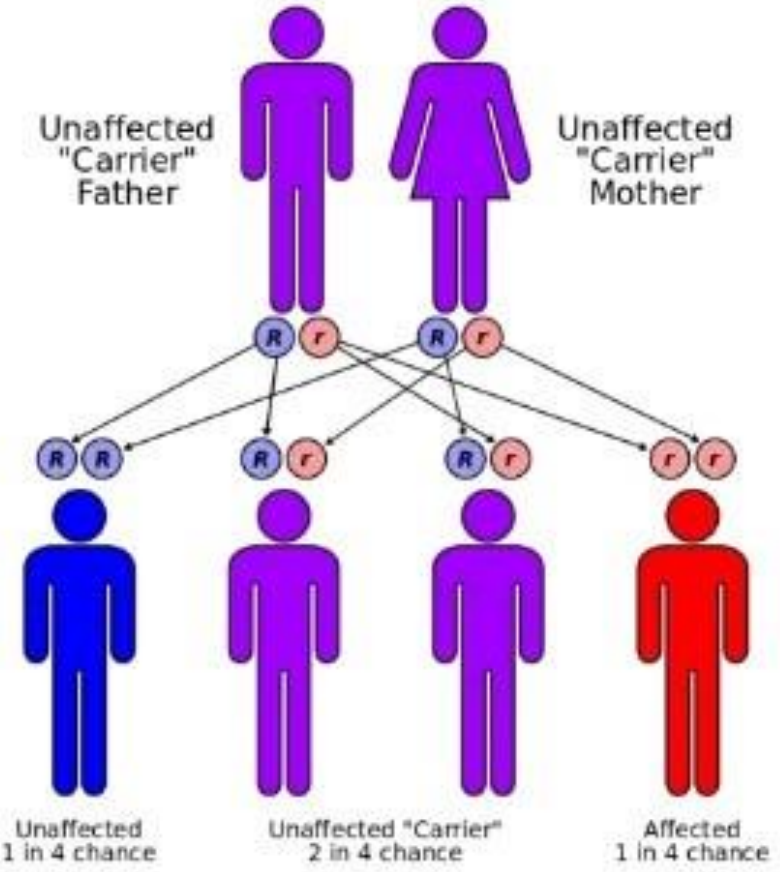


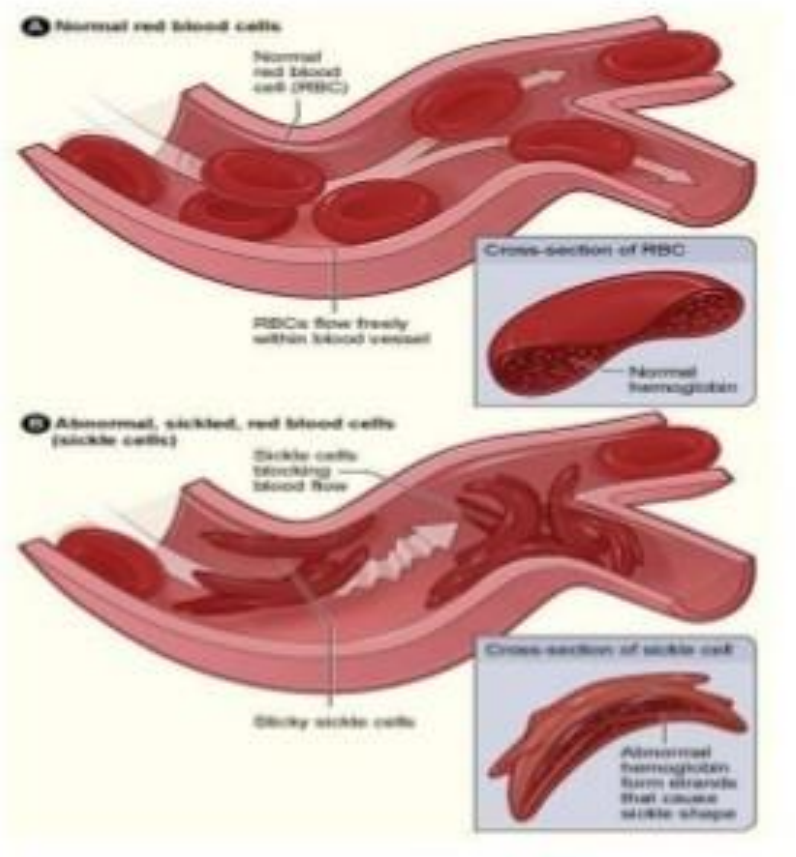
- An inherited, chronic disease in which the red blood cells, normally disc-shaped, become crescent shaped. As a result, they function abnormally and cause small blood clots. These clots give rise to recurrent painful episodes called "sickle cell pain crises".

- Formed by abnormal Hb genes aquired from carrier parents
- Carrier has only one affected copy of Hb gene

Sickle Cell

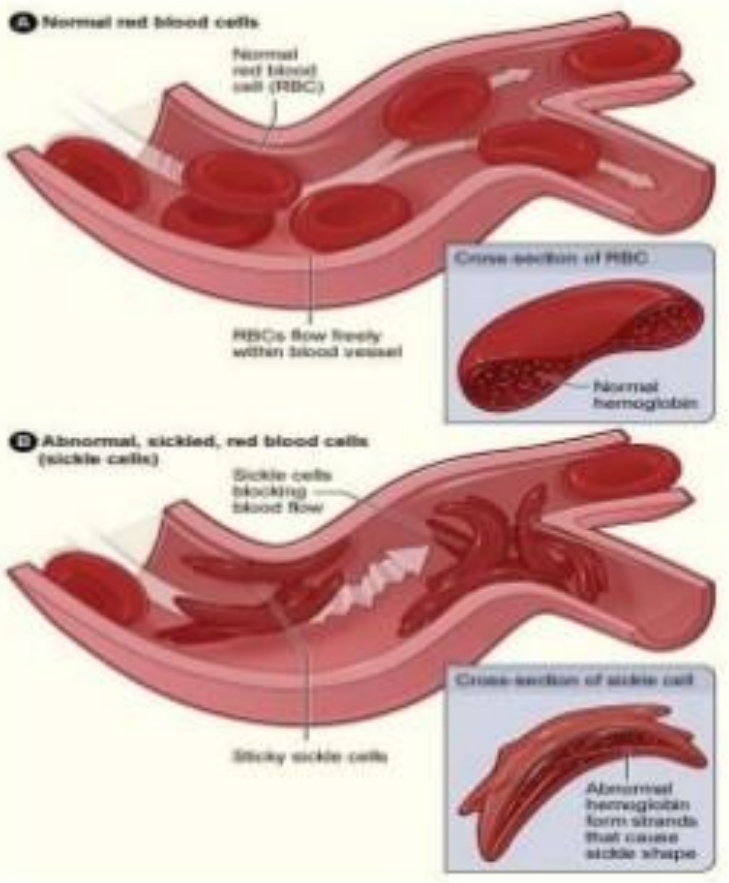
- **Sickle cell disease is most commonly found in African American populations. This disease was discovered over 80 years ago, but has not been given the attention it deserves.**




A Normal red blood cells
Normal red blood cell (RBC)
RBCs flow freely within blood vessel
Cross-section of RBC
Normal hemoglobin
B Abnormal, sickled, red blood cells (sickle cells)
Sickle cells blocking blood flow
Sticky sickle cells
Cross-section of sickle cell
Abnormal hemoglobin form strands that cause sickle shape

Complications

- Increased risk of severe bacterial infections due to loss of functioning spleen tissue
- Silent stroke
- Stroke
- Pripism and infarction of the penis[
- excessive bilirubinproduction and precipitation due to prolonged haemolysis.
- Chronic renal failure due to sickle-cell nephropathy
- Osteomyelitis
- Pulmonary hypertension
- Leg ulcers
- eye proplems (proliferative retinopathy, vitreous haemorrhages)

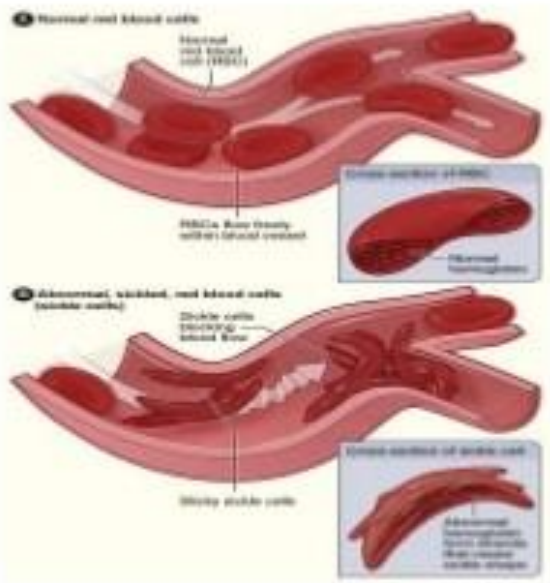

A Normal red blood cells
Normal red blood cell (RBC)
RBCs flow freely within blood vessel
Cross-section of RBC
Normal hemoglobin
B Abnormal, sickled, red blood cells (sickle cells)
Sickle cells blocking blood flow
Sticky sickle cells
Cross-section of sickle cell
Abnormal hemoglobin form strands that cause sickle shape

PLZ Donate !!! U could save them

Ttt:

- **Folic acid (1 gm life time)**
- **penicillin (5y)**
- If living in malarial countries should receive **anti-malarial chemoprophylaxis** for life.
- Vaso-occlusive crisis **: Opioids , NSAID .**
- Acute chest crisis : **oxygen supplementation for hypoxia , blood transfusion or exchange transfusion.**

- **Transfusion therapy :** Blood transfusions are often used in the management of sickle-cell disease in acute cases by adding normal red blood cells . reduces the risk of recurrent stroke and additional silent strokes



- **Bone marrow transplants .**

#5 - Von Willebrand disease :

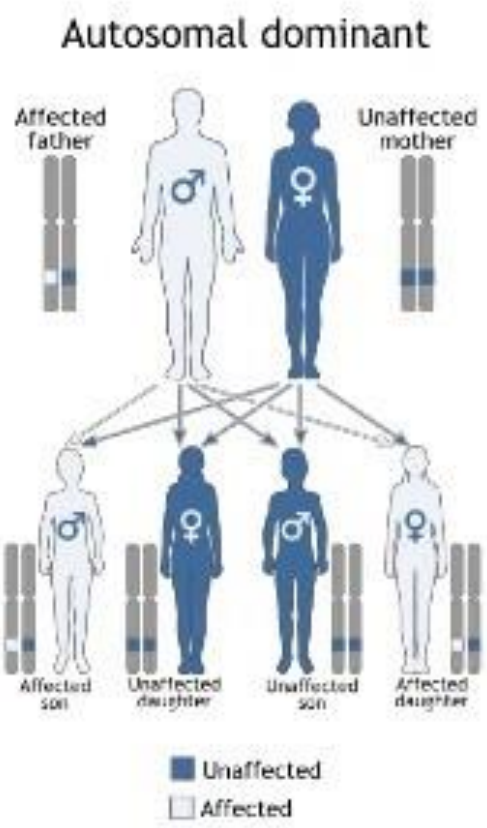
- the most common hereditary coagulation abnormality described in humans, although it can also be acquired as a result of other medical conditions (auto antibodies) .
- arises from a qualitative or quantitative deficiency of von Willebrand factor (vWF), a multimeric protein that is required for platelet adhesion

- three forms of vWD: hereditary, acquired, and pseudo or platelet type

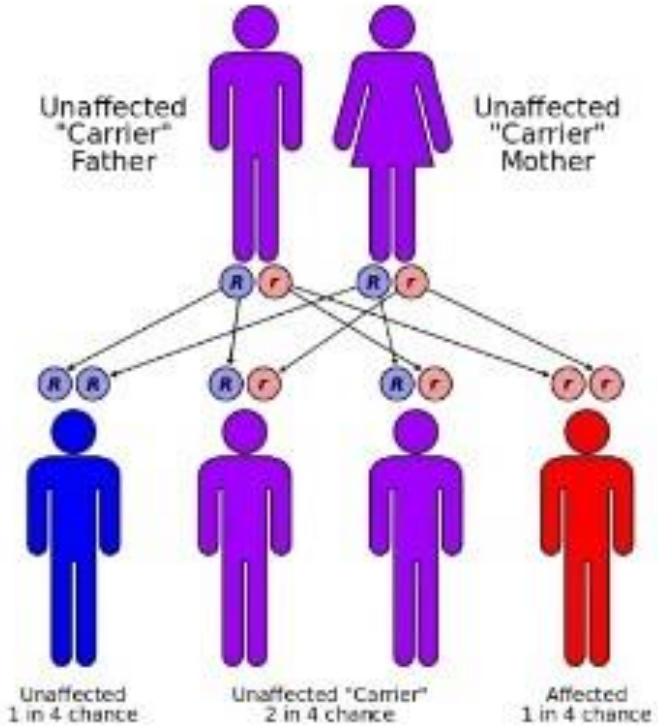
- There are three types of hereditary vWD: vWD Type I (most common) , vWD Type II, and vWD Type III

- Within the three inherited types of vWD there are various subtypes 2a , 2b , 2m , 2n

Type 1,2



Type 3



- The prevalence of vWD is about 1 in 100 individuals.[11] However the majority of these people do not have symptoms. The prevalence of clinically significant cases is 1 per 10,000
- most forms are rather mild, they are detected more often in women, whose bleeding tendency shows during menstruation

VON WILLEBRAND DISEASE

MOST COMMON INHERITED BLEEDING DISORDER

VON WILLEBRAND FACTOR (VWF) ACTS AS A CARRIER PROTEIN FOR FACTOR VIII IN PLASMA

VWF ALSO HELPS WITH PLATELET AGGREGATION AND ADHESION TO DAMAGED ENDOTHELIUM

TYPE 1: DEFICIENCY OF VWF (MOST COMMON TYPE)

TREATMENT: DESMOPRESSIN OR CRYOPRECIPITATE

PATIENTS MAY PRESENT WITH MUCOCUTANEOUS BLEEDING (E.G., EPISTAXIS, EASY BRUISING, MENORRHAGIA, GI BLEEDING)

TYPE 2: ABNORMAL AND DYSFUNCTIONAL VWF

TYPE 3: VWF IS ABSENT

TREATMENT: FACTOR VIII CONCENTRATE OR CRYOPRECIPITATE

www.medcomic.com

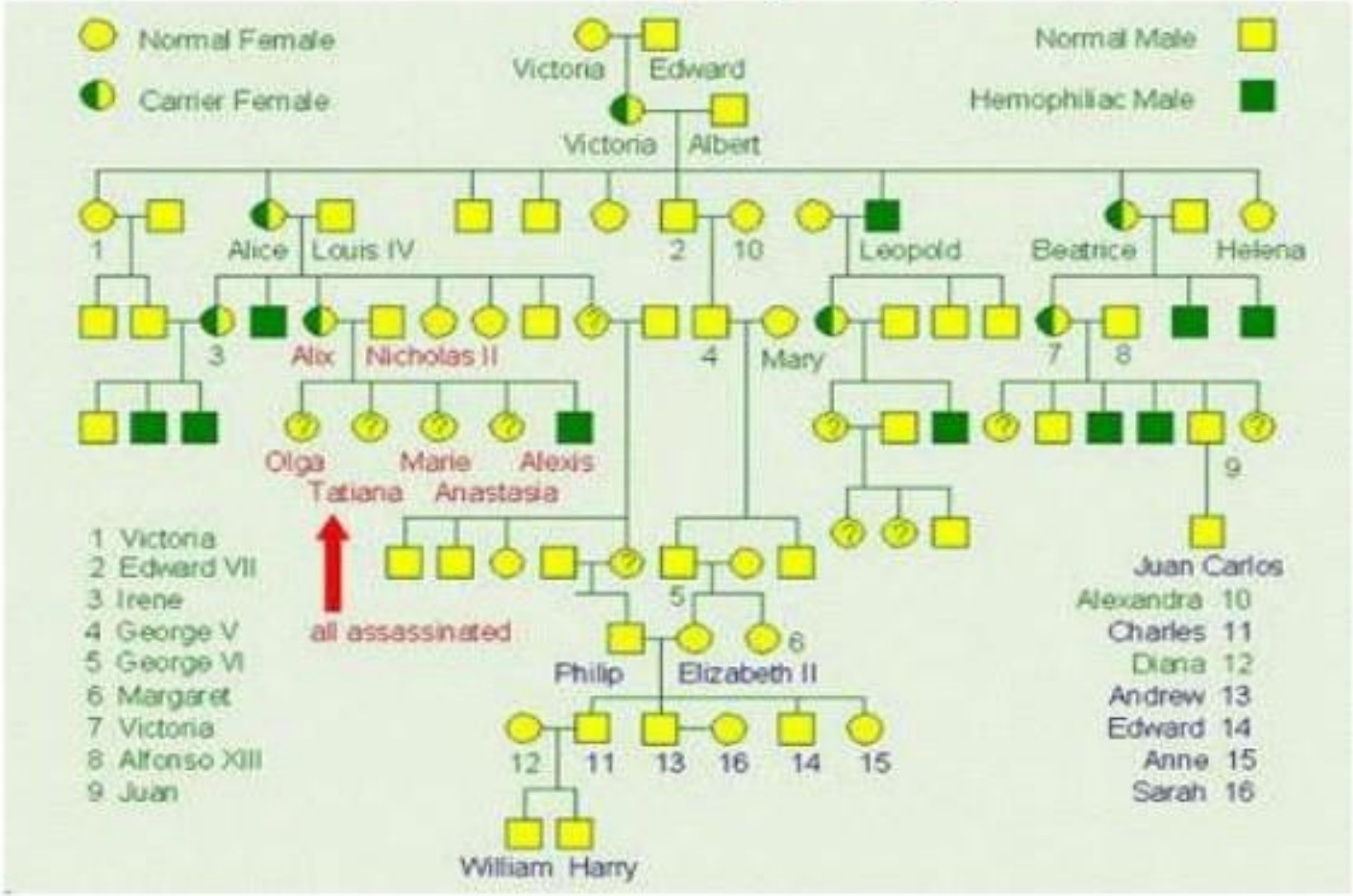
ttts

- Topical thrombin JMI and Topical Tisseel VH for wounds
- antifibrinolytic agents (Tranexamic acid) for clinical haemorrhage
- Blood transfusions for anemia and hypovolemia
- Desmopressin (DDAVP) . Type 1,2a

6 - Hemophilia, the royal disease

- Hemophilia is the oldest known hereditary bleeding disorder.
- Caused by a recessive gene on the X chromosome.
- There are about 20,000 hemophilia patients in the United States.
- One can bleed to death with small cuts.
- The severity of hemophilia is related to the amount of the clotting factor in the blood. About 70% of hemophilia patients have less than one percent of the normal amount and, thus, have severe hemophilia.
- Factor VIII deficiency
- Less prevelance in female

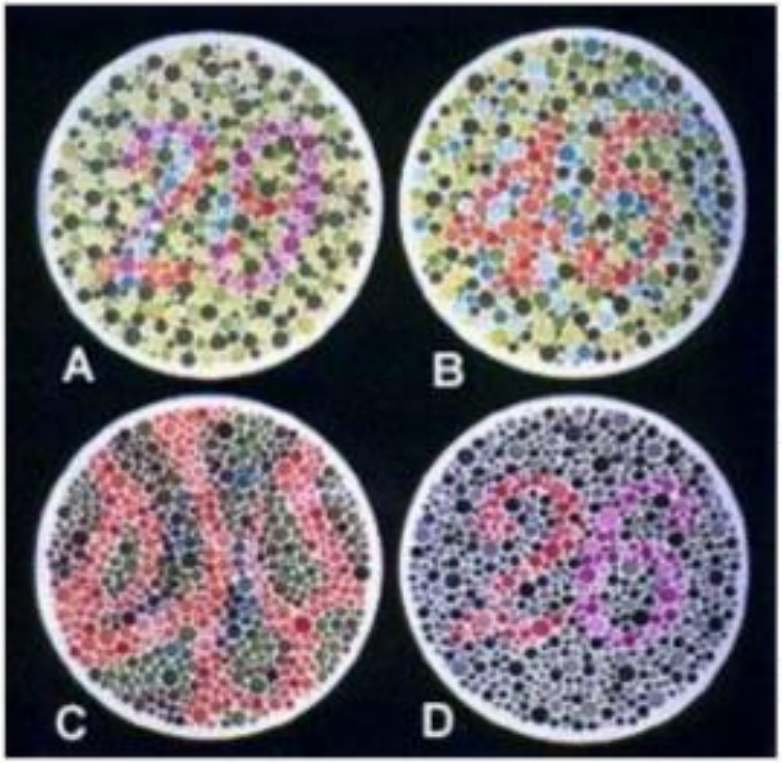
X-linked Inheritance pedigree chart



Ttt :

- Factor VIII concentrate
- Xyntha (anti hemolytic)
- Gene therapy
- Preventive excersices
- Alternative therapy (hypnosis)
- Avoid hymolytic drugs (Asprin , heparin , ….)

#7 - Color Blindness



- Cause: x-linked recessive
- 1/10 males have, 1/100 females have.
- Individuals are unable to distinguish shades of red-green.
- Are you color blind?

Monochromacy :

- (and thus the person views everything as if it were on a black and white television)

  - ***Rod monochromacy*** : exceedingly rare, nonprogressive inability to distinguish any colors as a result of absent or nonfunctioning retinal cones

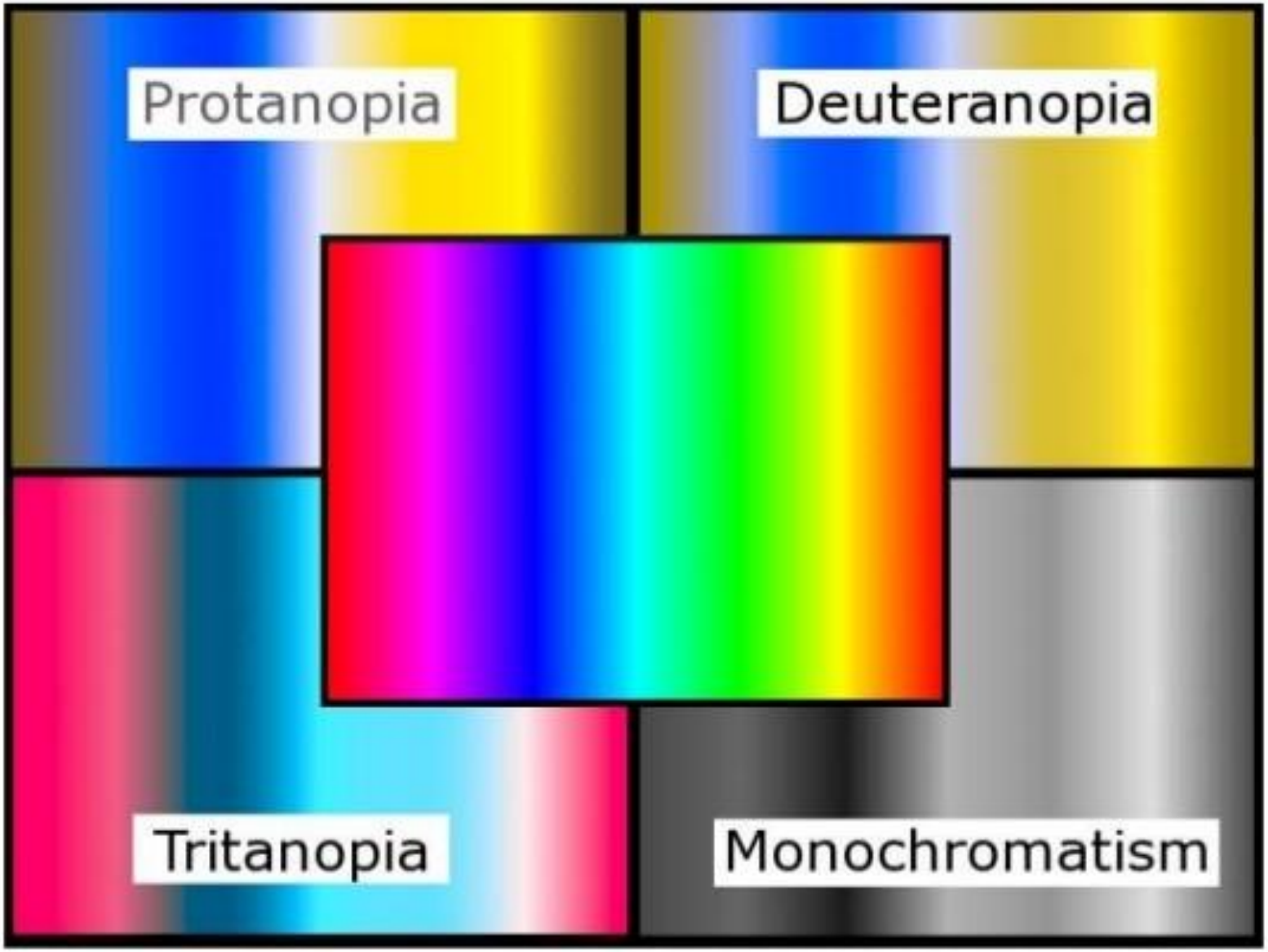
  - ***Cone monochromacy :*** a rare total color blindness that is accompanied by relatively normal vision, electroretinogram, and electrooculogram

Dichromacy :

- moderately severe color vision defect in which one of the three basic color mechanisms is absent or not functioning
- Dichromacy occurs when one of the cone pigments is missing and color is reduced to two dimensions
- "first" (*prout*:referring to the red photoreceptors), "second" (*deuter-*, the green), or "third" (*trit-*, the blue) photoreceptors are affected.

- Protanopia : perceive light wavelengths from 400 to 650 nm so no pure red !
- Deuteranopia : the green retinal photoreceptors are absent
- Tritanopia : total absence of blue retinal receptors. Blues appear greenish, yellows and oranges appear pinkish .

- Protanopia : perceive light wavelengths from 400 to 650 nm so no pure red !
- Deuteranopia : the green retinal photoreceptors are absent
- Tritanopia : total absence of blue retinal receptors. Blues appear greenish, yellows and oranges appear pinkish .


Protanopia
Deuteranopia
Tritanopia
Monochromatism

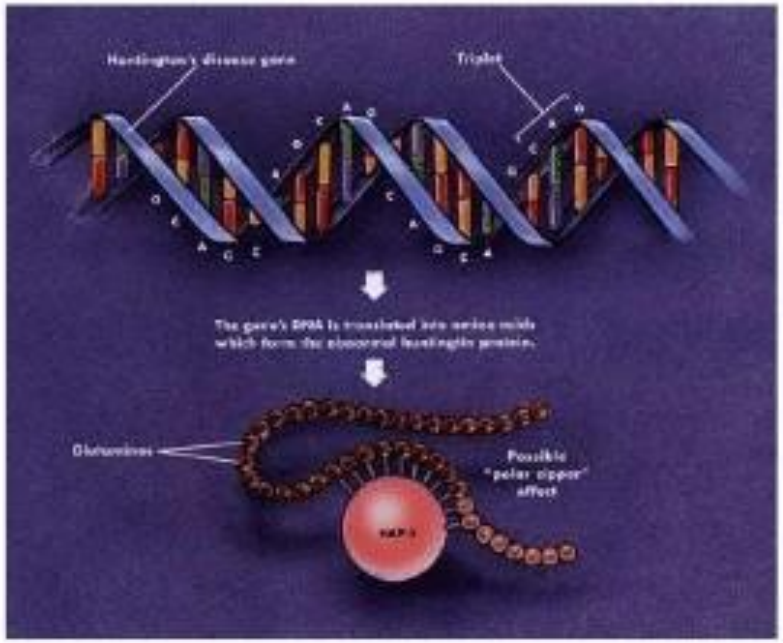
Trichromacy :

- Protanomaly : altered spectral sensitivity of red retinal receptors so poor red–green hue discrimination .
- Deuteranomaly : shift in the green retinal receptors , the most common type of color vision deficiency, mildly affecting red–green hue discrimination 5% of Eu. Males.
- Tritanomaly : rare, hereditary color vision deficiency affecting blue–green and yellow–red/pink hue discrimination

#8 - Huntington's Disease

- Huntington's disease (HD) is an inherited, degenerative brain disorder which results in an eventual loss of both mental and physical control. The disease is also known as Huntington's chorea. Chorea means "dance-like movements" and refers to the uncontrolled motions often associated with the disease.

Huntington's



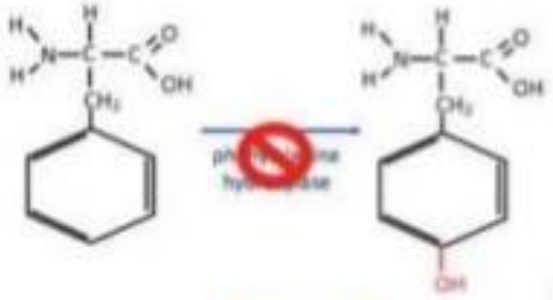
- Looking back at the pedigree chart is Huntington's dominant or recessive?
- Scientists have discovered that the abnormal protein produced by the Huntington's disease gene, which contains an elongated stretch of amino acids called glutamines, binds more tightly to HAP-1 than the normal protein does.

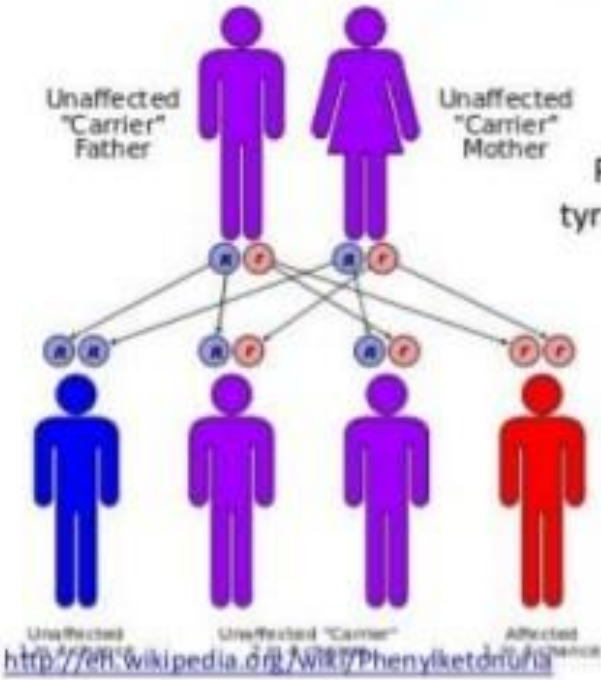
9 - Phenylketonuria or PKU

People with PKU cannot consume any product that contains aspartame.

PKU is a metabolic disorder that results when the PKU gene is inherited from both parents (recessive or dominant? Monogenic or chromosomal?)

- inborn error of metabolism involving impaired metabolism of phenylalanine, one of the amino acids. Phenylketonuria is caused by absent or virtually absent phenylalanine hydroxylase (PAH) enzyme activity.





http://en.wikipedia.org/wiki/Phenylketonuria

Phenylketonuria (PKU)

Inherited, progressive, degenerative.

Cause

Autosomal recessive, disease-causing allele: mis-sense base-substitution mutation on the gene for the enzyme ***phenylalanine hydroxylase***.

Result

Phenylalanine (Phe) cannot be metabolised into tyrosine. Phe builds up in the brain, and competes with other amino-acids related to transport.

Effect

Mental development is retarded.

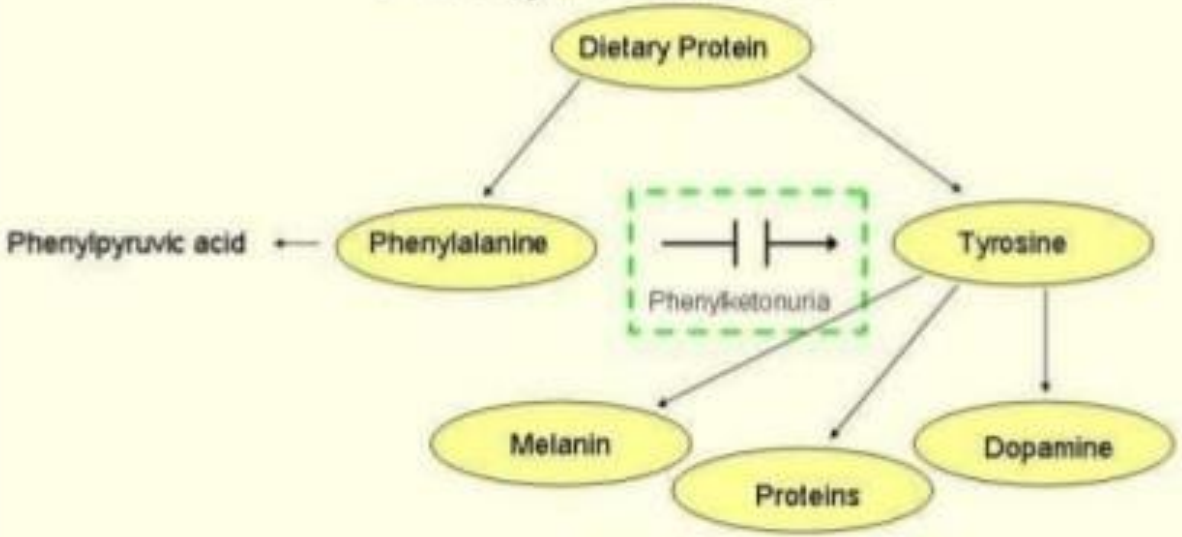
Detection

Heel-prick (Guthrie test) of newborns to test concentration of Phe and Phe:Tyr ratio.

PKU

- Phenylalanine is an essential amino acid and is found in nearly all foods which contain protein, dairy products, nuts, beans, tofu… etc.
- A low protein diet must be followed.
- Brain damage can result if the diet is not followed causing mental retardation…and mousy body odor (phenylacetic acid is in sweat).

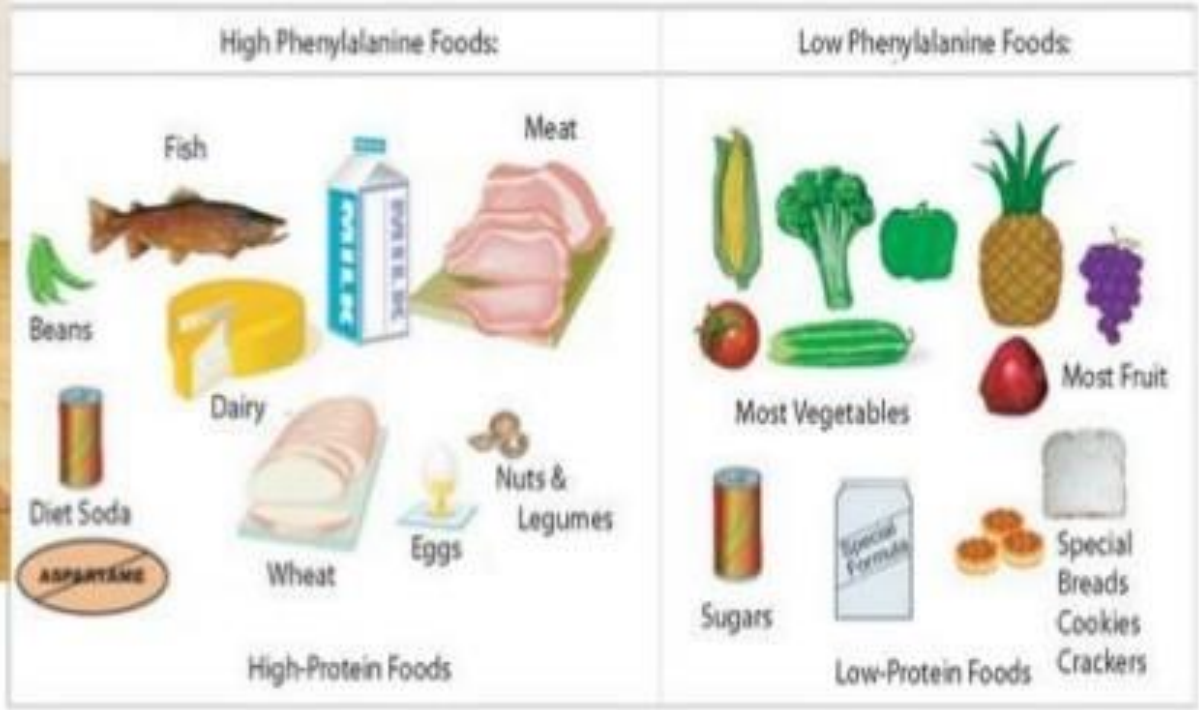
Phenylketonuria



- **Lack of phenylalanine hydroxylase blocks the transformation of phenylalanine into tyrosine**
- **Unmetabolized phenylalanine is shunted into the pathway that leads to the formation of phenylketones**
- **Excess phenylalanine also inhibits the formation of melanin from tyrosine**

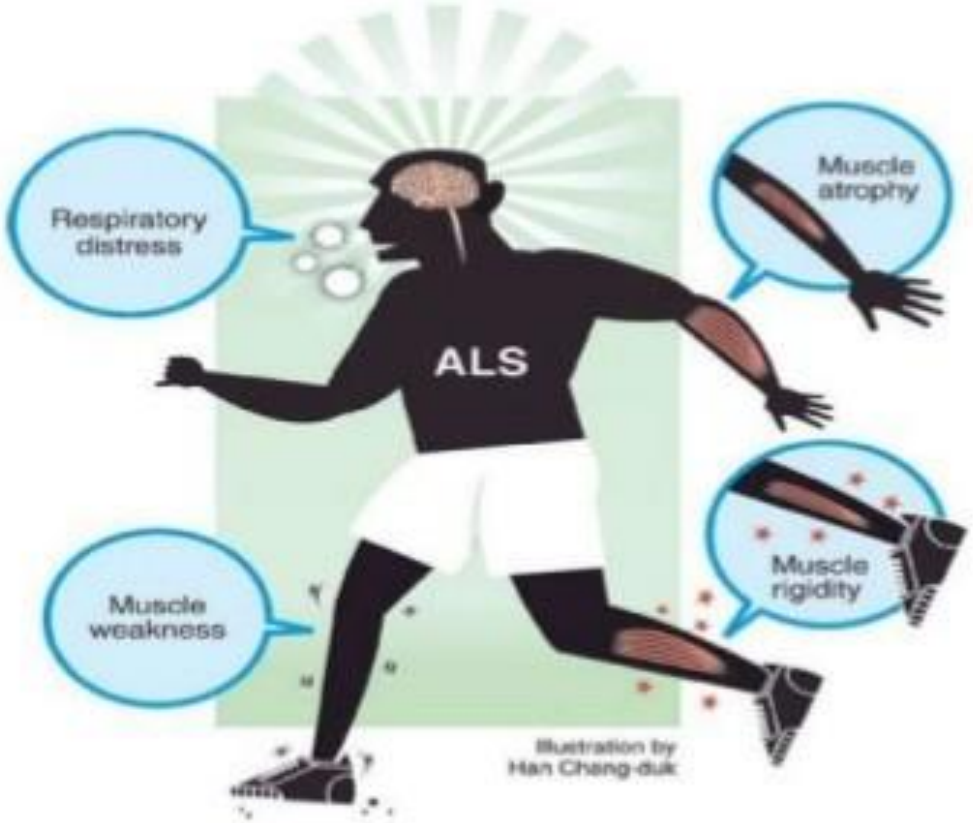
Phenylalanine.

Free diet

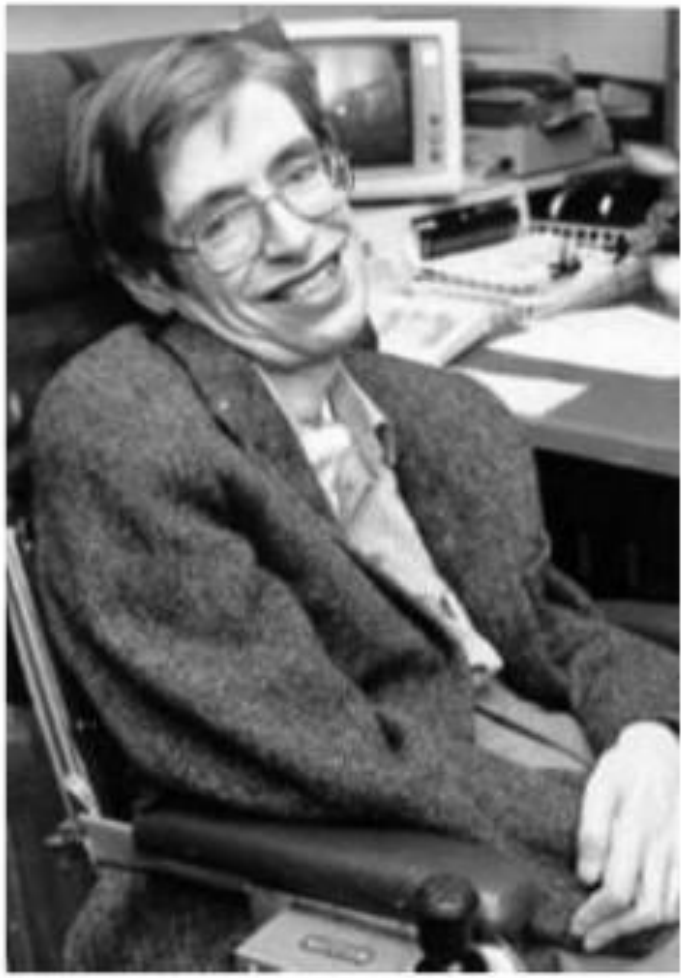


10 - ALS
(Amyotrophic Lateral Sclerosis, or Lou Gehrig's disease)

- Autosomal
- Dominant



Stephen Hawking ??!!!



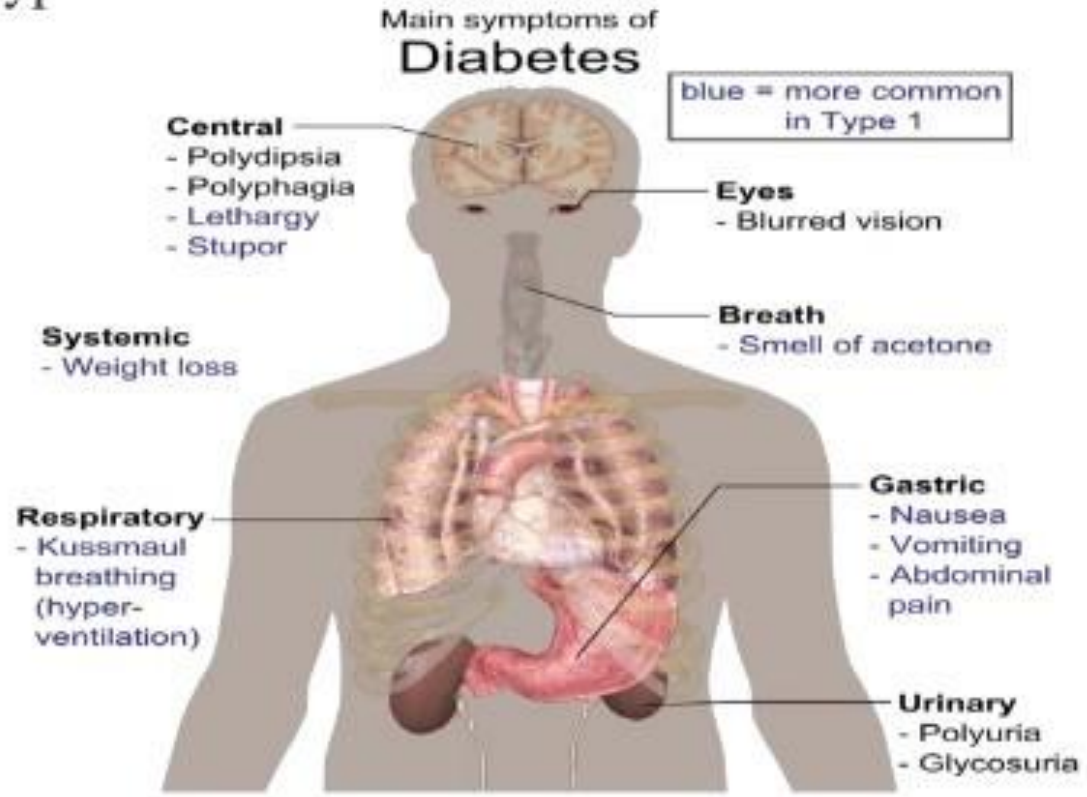
the fourth cosmology theor y by union of general theory of relativity and quantum mechanics

The theory of every thing . 2014 movie

- the disease strikes people between the ages of 40 and 70, and as many as 30,000 Americans have the disease at any given time
- This monogenic mutation is believed to make a defective protein that is toxic to motor nerve cells.
- A common first symptom is a painless weakness in a hand, foot, arm or leg, other early symptoms include speech swallowing or walking difficulty

Diabetes

- Type 1 reveals itself in childhood with polygenic disorders , Type 2 can be made worse from excessive lifestyle



- Warning signs of diabetes :
  - Extreme thirst
  - Blurry vision from time to time
  - Frequent urination
  - Unusual fatigue or drowsiness
  - Unexplained weight loss

  - Diabetes is the leading cause of kidney failure, blindness, and amputation in adults, and can also lead to heart disease.

#12 - Albinism

- Patients are unable to produce skin or eye pigments, and thus are light-sensitive
- congenital disorder characterized by the complete or partial absence of pigment in the skin, hair and eyes due to absence or defect of tyrosinase which is a copper-containing enzyme involved in the production of melanin
- Autosomal recessive

- no cure for Albinism , just be away from sun and regularly visit the dermatologist , dark glasses and dark contact lenses

13 - Achondroplasia

Achondroplasia (a.k.a. dwarfism)

- Monogenic, autosomal
  - Carriers express genes , so it is recessive

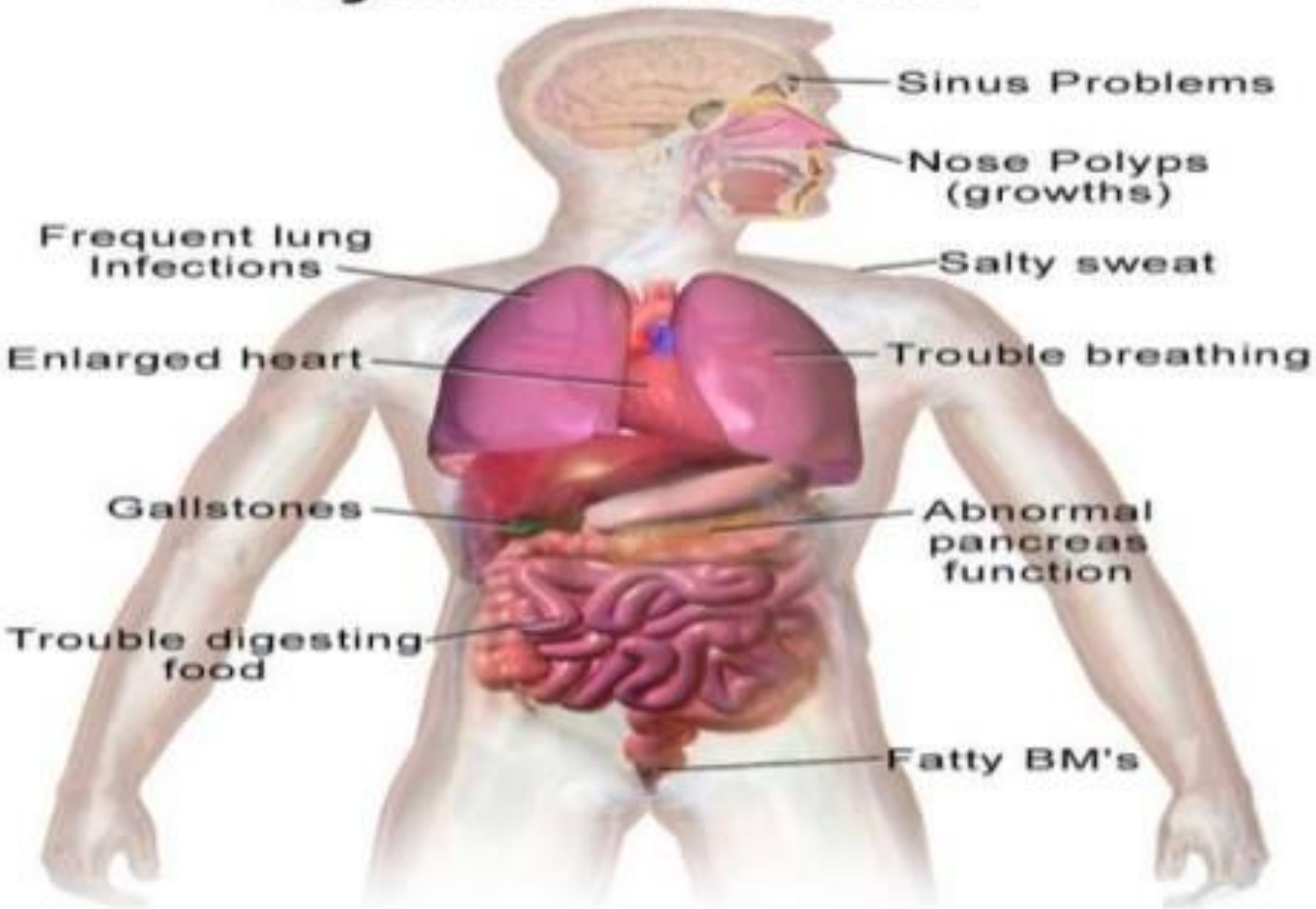
  - Ttt:

  GH , thyroid injection

16 - Cystic Fibrosis (CF)

- Monogenic autosomal recessive (by carriers)
- Cause: deletion of only 3 bases on chromosome 7
- Fluid in lungs, potential respiratory failure
- Common among Caucasians…1 in 20 are carriers

Health Problems with Cystic Fibrosis



17 - Muscular Dystrophy

- **What Is Muscular Dystrophy?**
  Muscular dystrophy is a disease in which the muscles of the body get weaker and weaker and slowly stop working because of a lack of a certain protein
- Can be passed on by one or both parents, depending on the form of MD (therefore is autosomal both dominant and recessive)

Very rare genetic disorders

- Cri du chat (deletion chromosome #5)
- Prader willi syndrome (chromosome #15)
- #18 Q deletion syndrome
- Hereditary hemochromatosis
- Marfen syndrome

I'm So Tired

THANX a lot