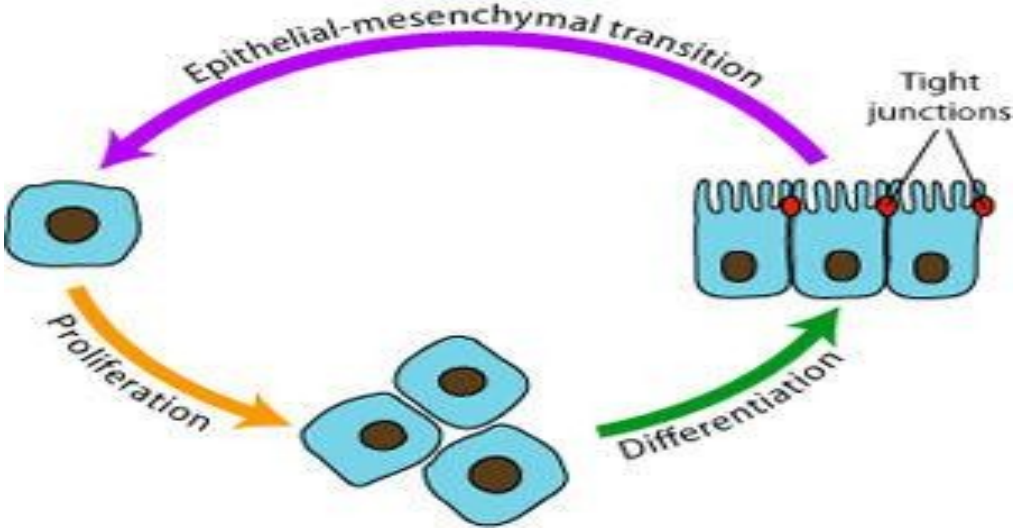
# INTRODUCTION TO MOLECULAR REGULATION & SIGNALING





# INTRODUCTION

- MOLECULAR GENETICS
- GENE TRANSCRIPTION
- INDUCTION & ORGAN FORMATION
- EPITHELIAL MESENCHYMAL INTERACTIONS
- CELL SIGNALING & GDFs

# Molecular genetics



- Is the field of biology that studies the structure and function of genes at a molecular level.
- The field studies how the genes are transferred from generation to generation. Molecular genetics employs the methods of **genetics** and **molecular biology.**

- There are approximately **35,000 genes** in the human genome, which represents only a third of the number predicted prior to completion of the **Human Genome Project**.

# The Human Genome Project



Is a molecular genetics project that began in the 1990s and was projected to take fifteen years to complete. The project was started by the U.S. Department of Energy and the National Institutes of Health in an effort to reach six set goals.

# The goals of HGP

1. Identifying 20,000 to 25,000 genes in human DNA (although initial estimate were approx. 100,000 genes)
2. Determining sequences of chemical based pairs in human DNA
3. Storing all found information into databases
4. Improving the tools used for data analysis
5. Transferring technologies to private sectors
6. Addressing the ethical, legal, and social issues (ELSI) that may arise from the projects.

- The project was worked on by **eighteen** different countries.
- The collaborative effort resulted in the discovery of the many benefits of molecular genetics.
- **Discoveries** such as molecular medicine, new energy sources and environmental applications, DNA forensics, and livestock breeding, are only a few of the benefits that molecular genetics can provide.

# Gene expression

- Is the process by which information from a gene is used in the synthesis of a functional gene product.
- Several steps in the gene expression process may be modulated, including the transcription, RNA splicing, translation and post translational modification.

# GENE TRANSCRIPTION

# CHROMATIN

- Is a complex of DNA & protein



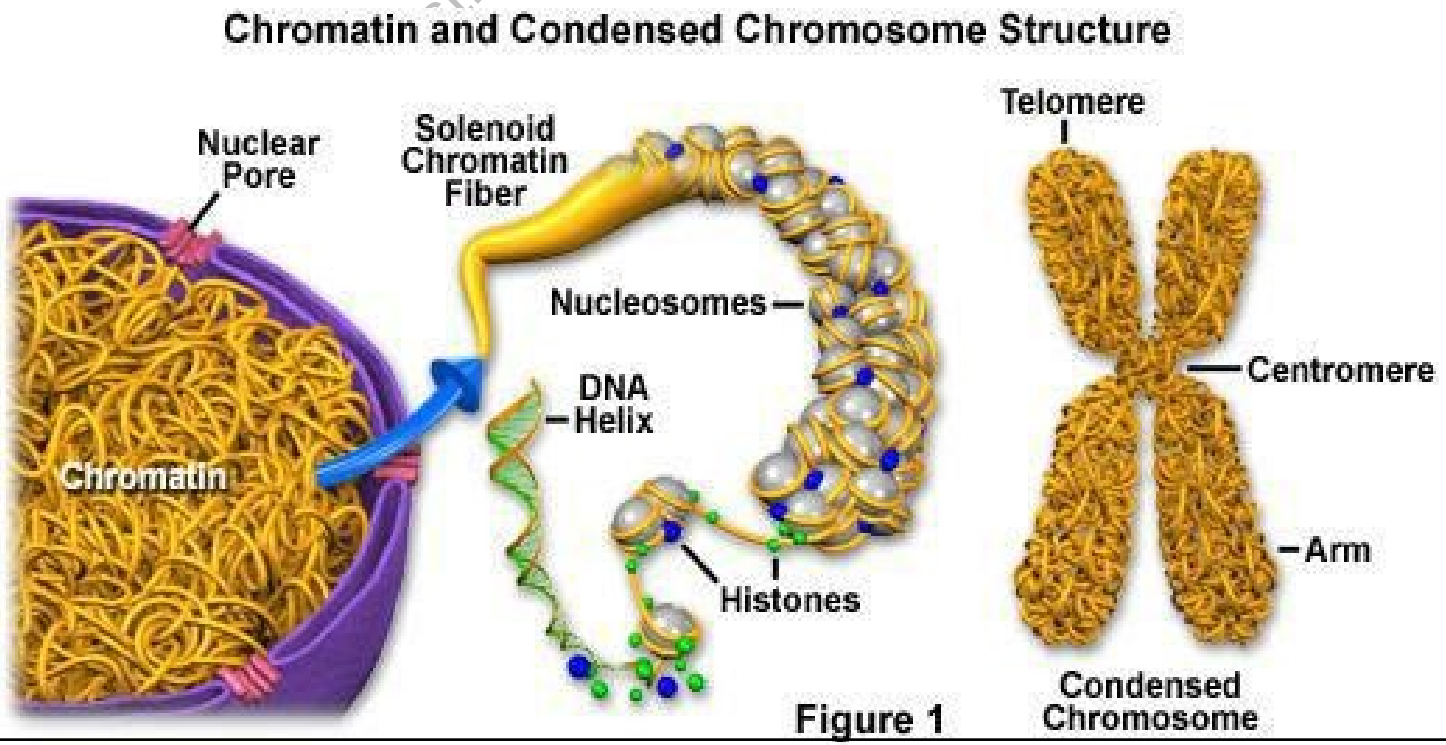
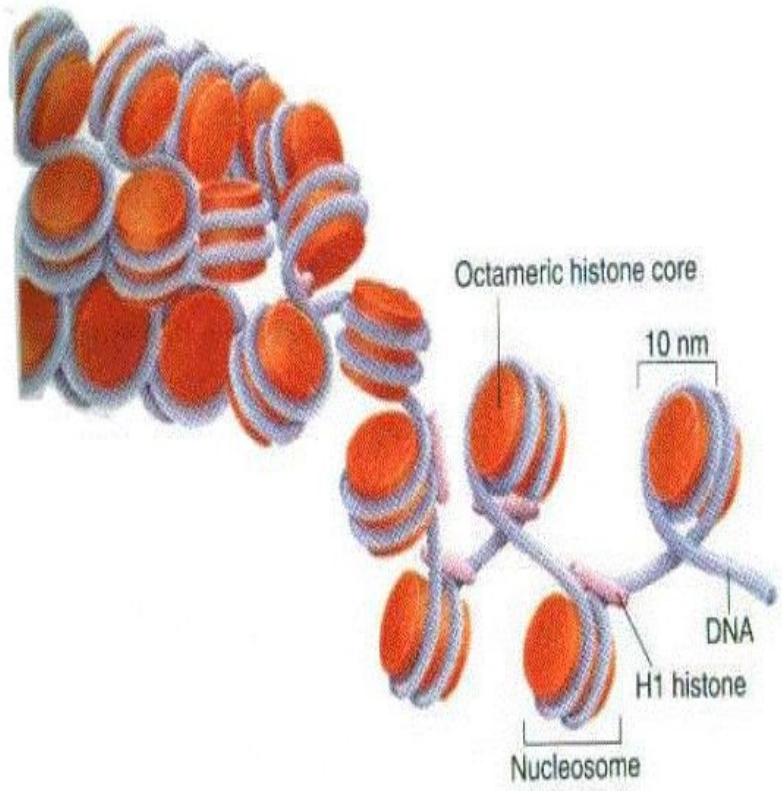



Figure 1

# NUCLEOSOME

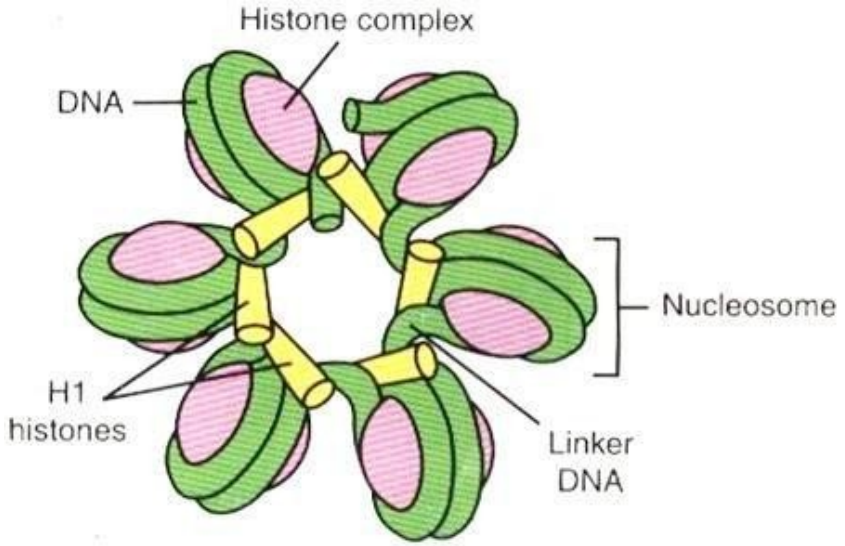
- Is the basic unit of structure of chromatin.
- Each DNA strand, having 140 base pairs, wraps around an octamer of histone proteins, forming a series of bead-like structures, called **nucleosomes.**



# Cont…

Thus nucleosomes are connected to each other by linker DNA and H1 histones that keeps the DNA tightly coiled, so that it cannot be transcribed



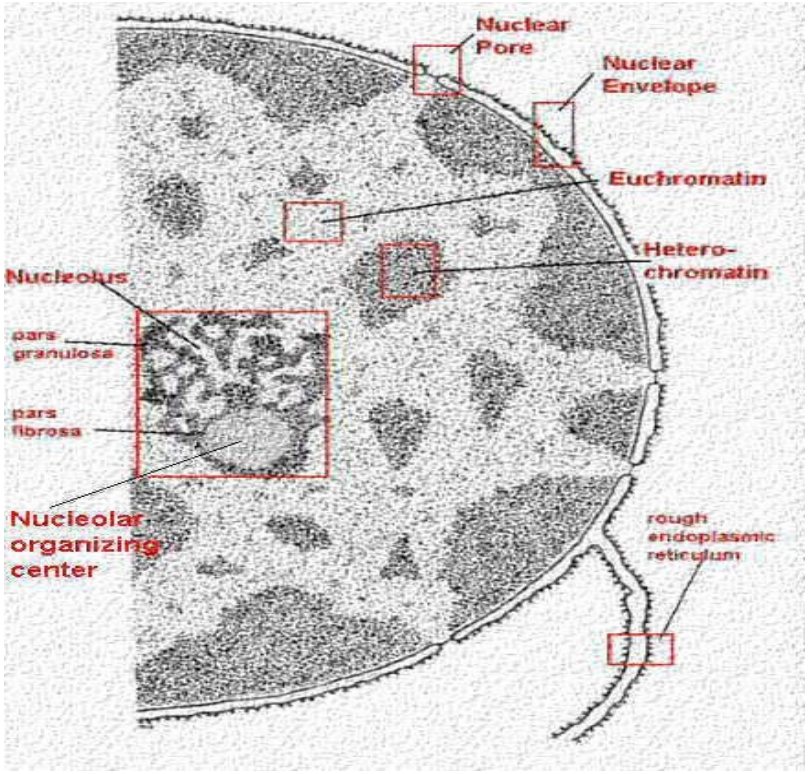



Drawing showing nucleosomes that form the basic unit of chromatin. Each nucleosome consists of an octamer of histone proteins and approximately 140 base pairs of DNA. Nucleosomes are joined into clusters by linker DNA and other histone proteins.

# TYPES OF CHROMATIN

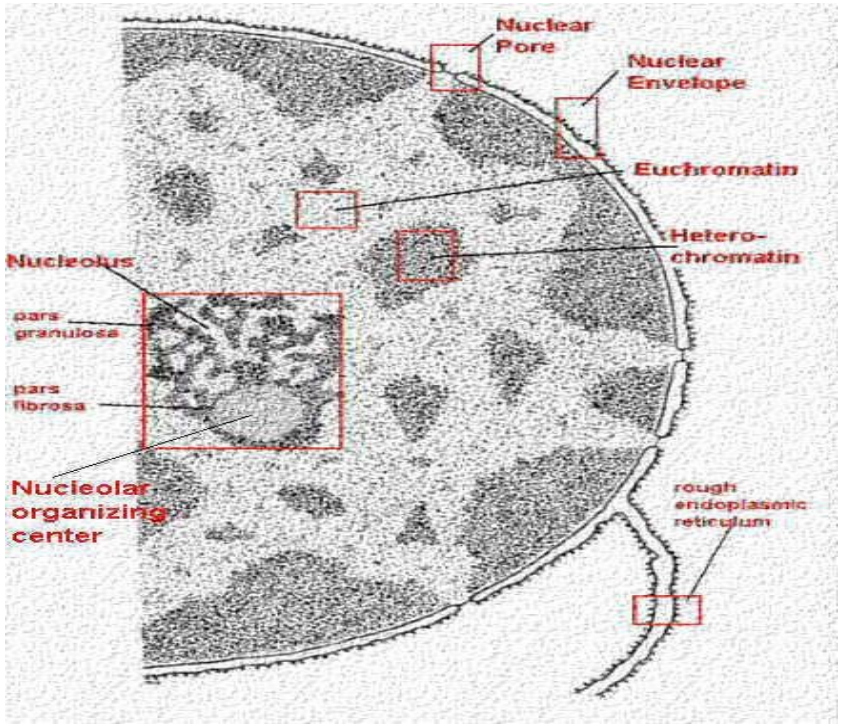
There are two types of chromatin.

- **Heterochromatin** is the more compact, condensed & tightly coiled form and contains DNA that is infrequently transcribed.



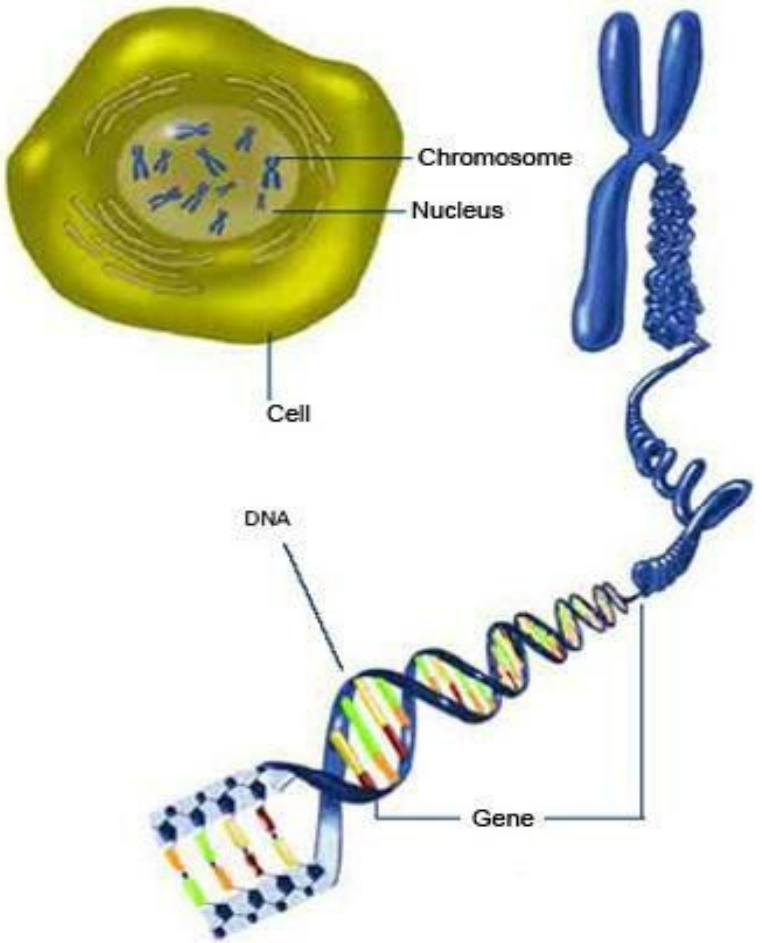
# TYPES OF CHROMATIN

- **Euchromatin** is the loosely packed, uncoiled, less condensed form of DNA, contains genes that are active or frequently expressed by the cell.



# GENES

- Genes are the hereditary determiners which reside with in the DNA strand.
- A particular gene can have multiple different forms, or alleles having different sequences of DNA.



# Regions of a Typical gene

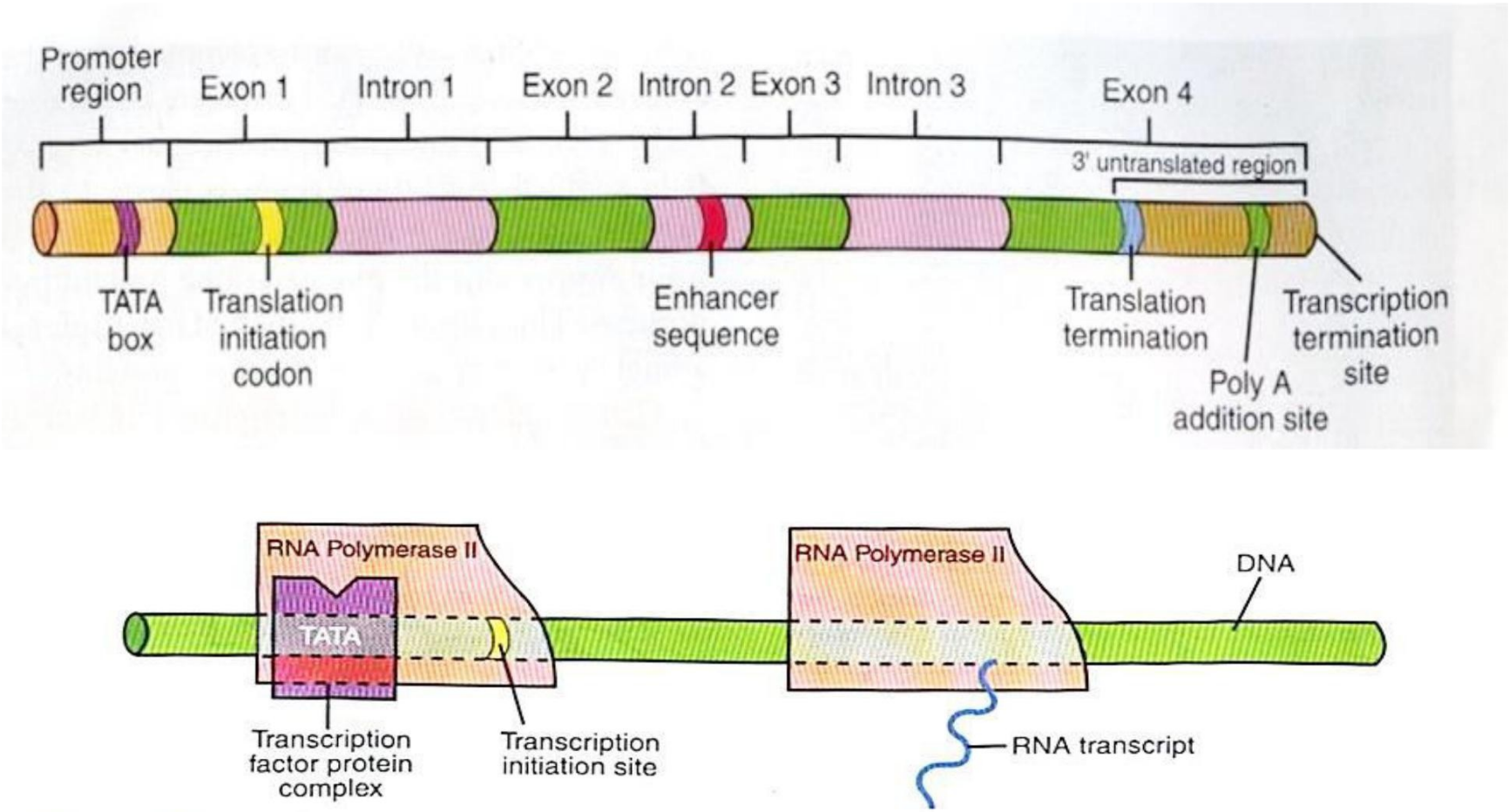


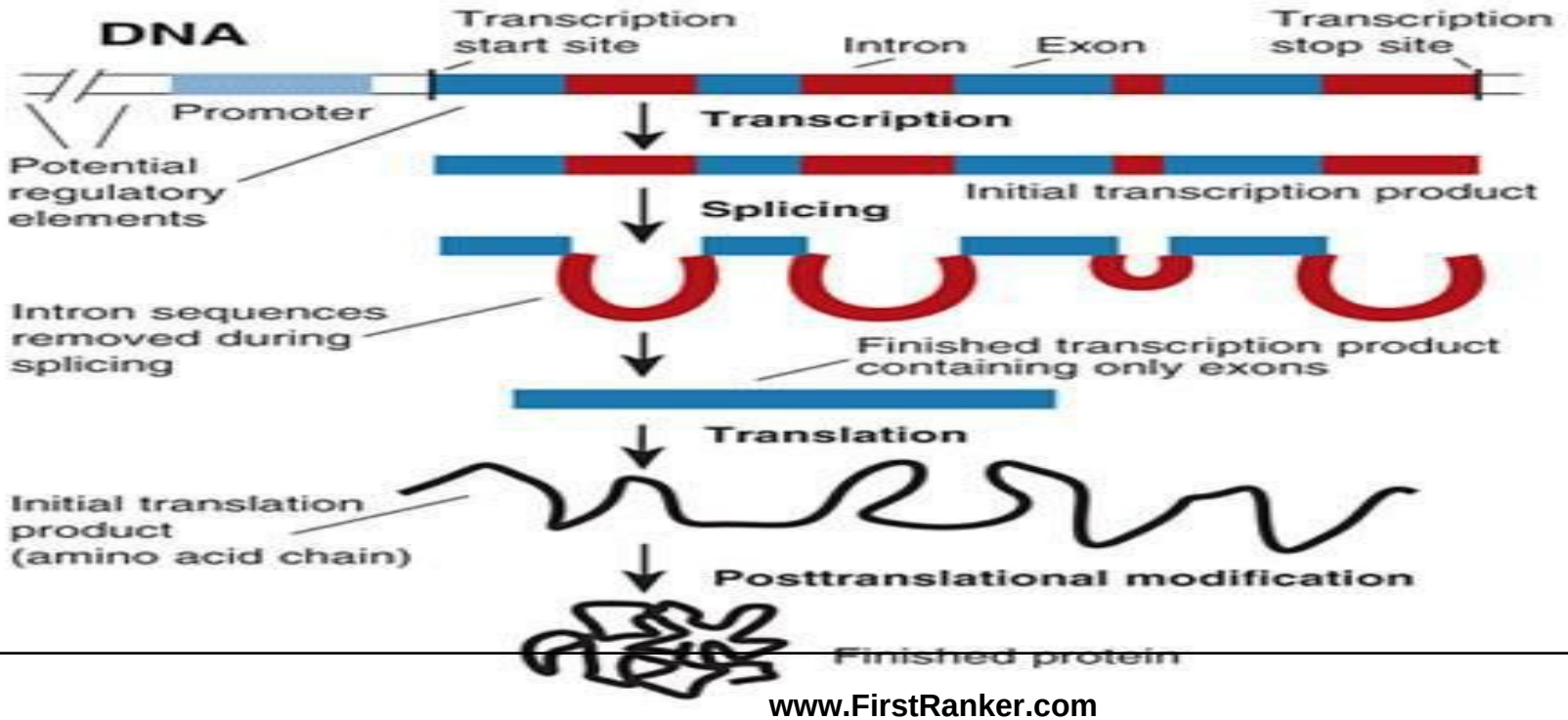

**Figure 1.5** Drawing showing binding of RNA polymerase II to the TATA box site of the promoter region of a gene. This binding requires a complex of proteins plus an additional protein called a transcription factor. Transcription factors have their own specific DNA binding domain and function to regulate gene expression.

# Protein synthesis

Requires two steps:

1. **Transcription**
2. **Translation**.

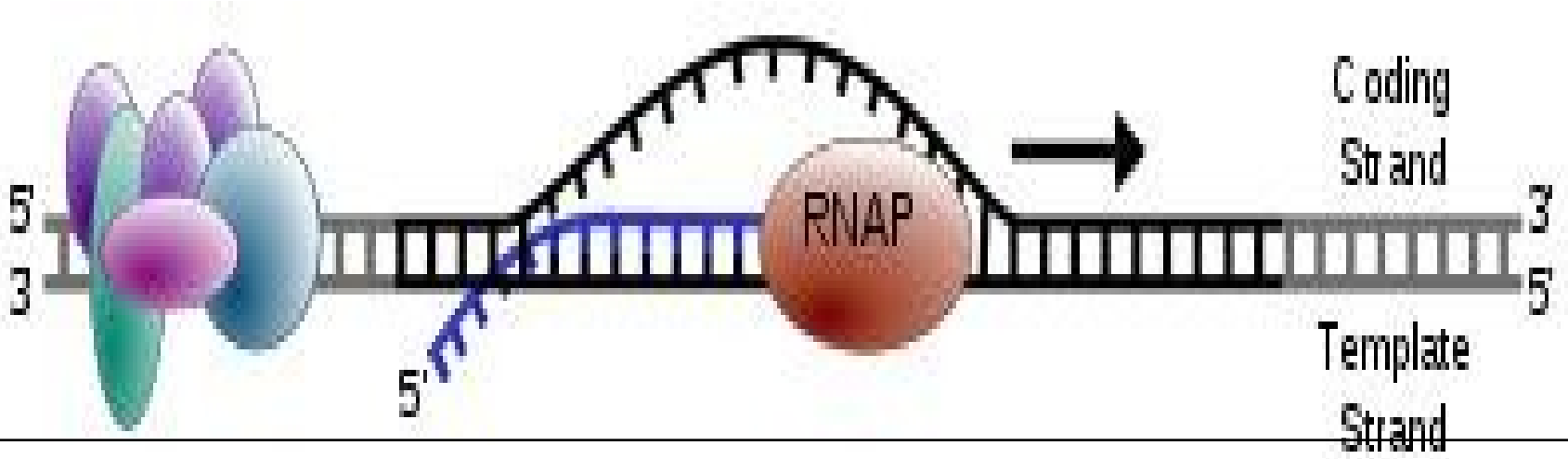




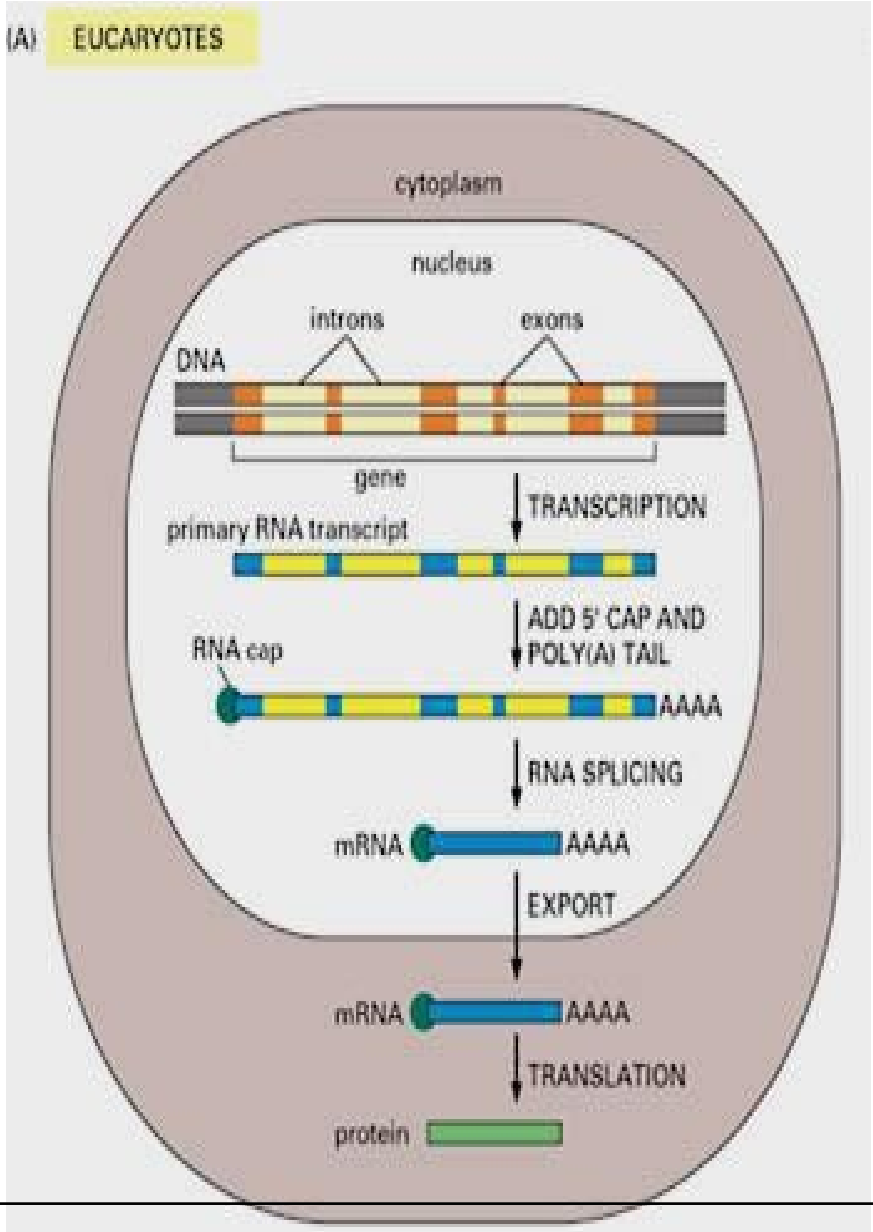
# TRANSCRIPTION

- A DNA strand is used to synthesize a strand of mRNA.
- Three bases in **DNA code** for one amino acid
- Only one strand of DNA is copied.
- A single gene may be transcribed thousands of times.
- After transcription, the DNA strands rejoin.

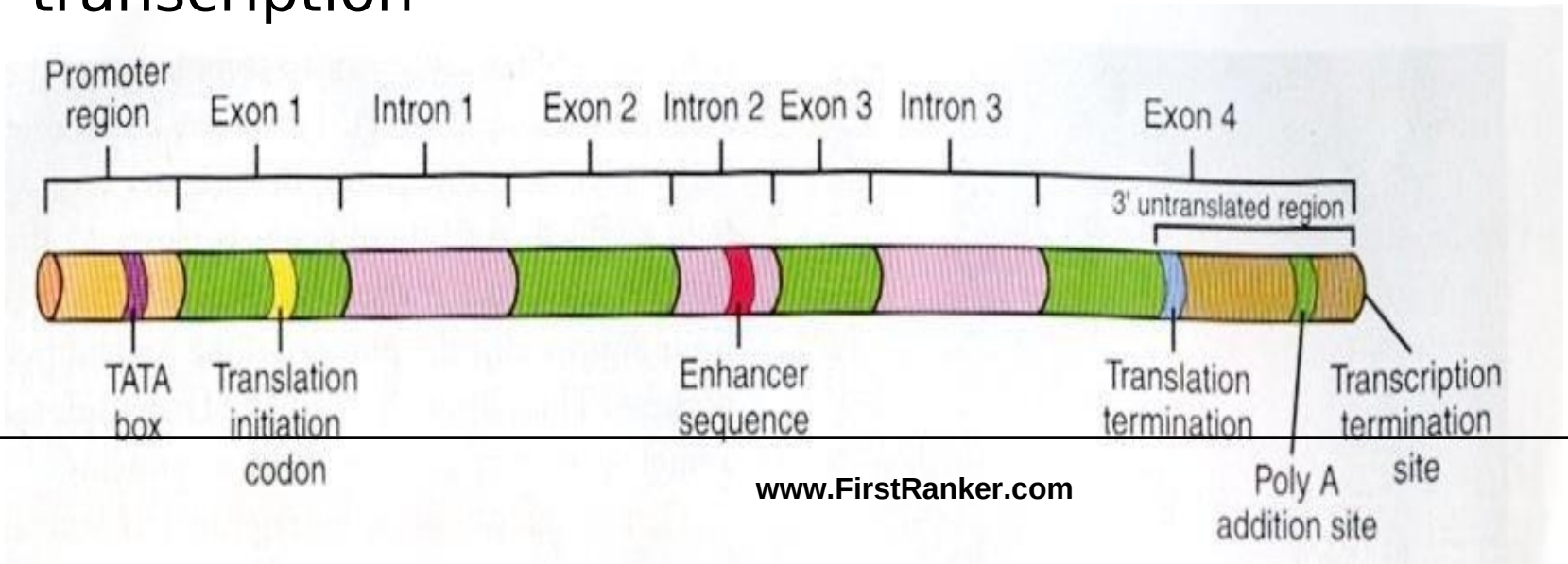




- Initial transcript of gene is nRNA or pre m RNA. is longer than mRNA because it contains introns that are to be removed or **spliced out.**
- Then mRNA moves from nucleus to cytoplasm.



- **Enhancers:** Regulatory elements of DNA that **activate utilization** of promoters, control their **efficiency** and **rate of transcription.**
- They can **reside any where** along the DNA strand.
- They are used to **regulate gene expression.**
- **Silencers:** Enhancers that can **inhibit** transcription



# Hypothetical gene

Showing alternative splicing to produce different proteins from same gene (Splicing isoforms)

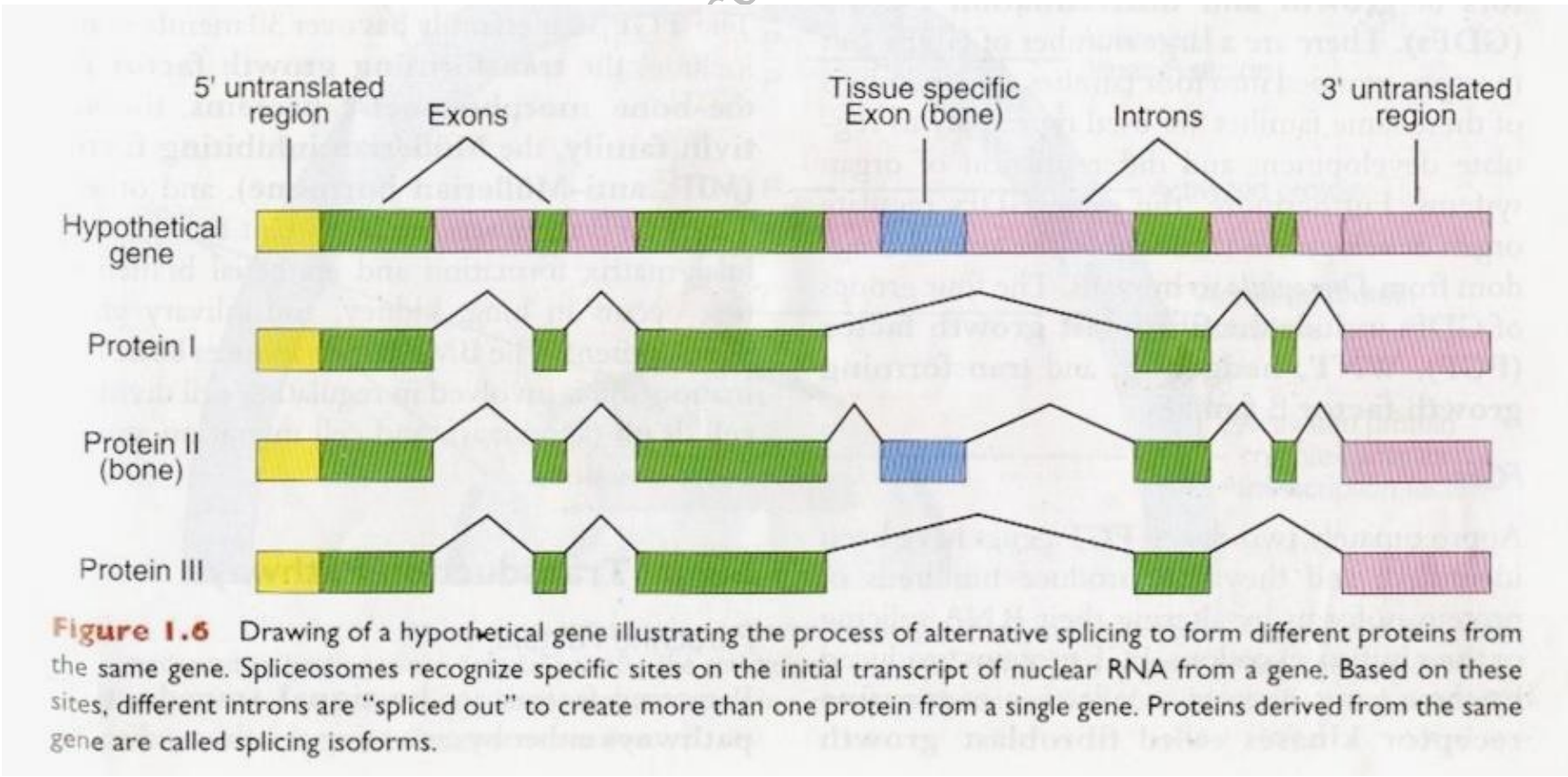
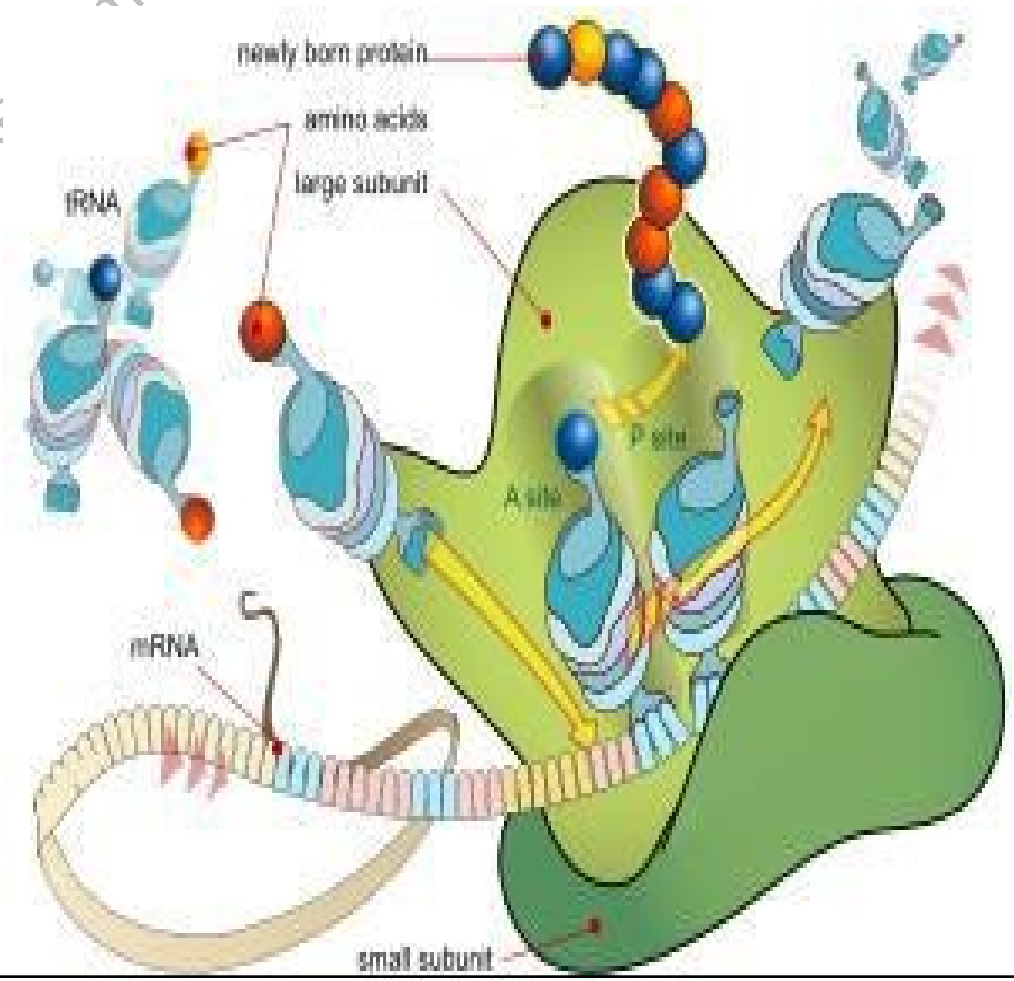



**Figure 1.6** Drawing of a hypothetical gene illustrating the process of alternative splicing to form different proteins from the same gene. Spliceosomes recognize specific sites on the initial transcript of nuclear RNA from a gene. Based on these sites, different introns are "spliced out" to create more than one protein from a single gene. Proteins derived from the same gene are called splicing isoforms.

# Translation

- tRNA charged with amino acid (3-letter ***ANTICODON*** ) enters the ribosome and aligns with the correct mRNA triplet (a ***CODON***). Ribosome then adds amino acid to growing protein chain.



# Induction and Organ Formation



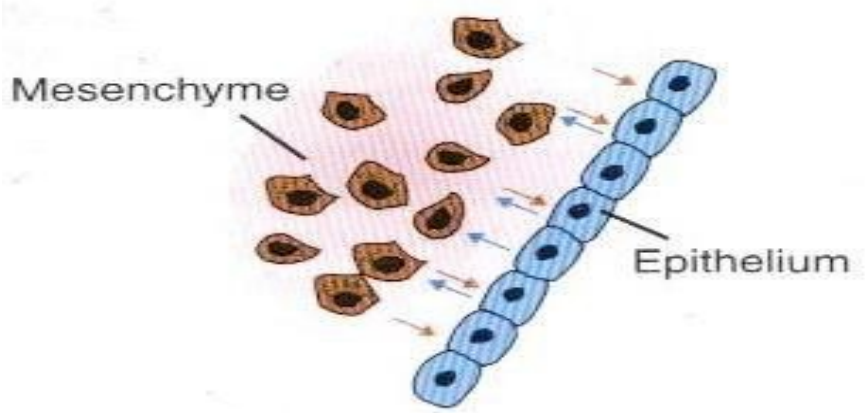
- Organs are formed by interactions between cells and tissues.
- One group of cells or tissues causes another set of cells or tissues to change their fate, a process called **Induction.**
- In each such interaction, one cell type or tissue is the **inducer** that produces a signal, and one is the **responder** to that signal.

# Cont…

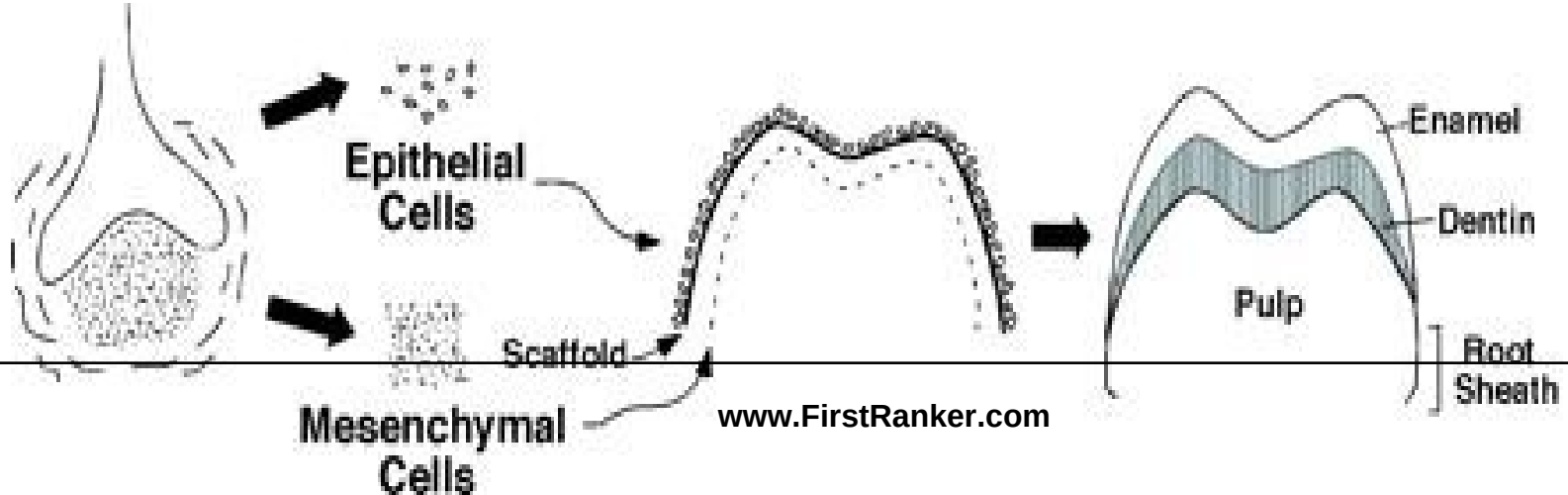
- **Competence**: Capacity to respond to a signal.
- **Competence factor** activates the responding tissue.

# Epithelial-mesenchymal interactions

- **Epithelial cells** are joined together in tubes or sheets, whereas **mesenchymal cells** are fibroblastic in appearance and dispersed in extracellular matrices.



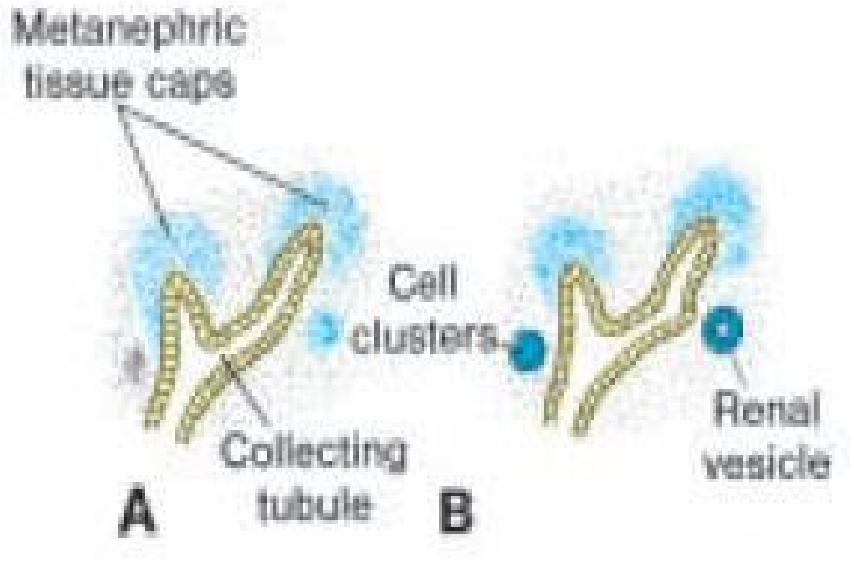


# Tooth development

# Cont….

- Endoderm of the ureteric bud and mesenchyme from the metanephric tissue to produce nephrons in the kidney.



# Cell Signaling



- Interaction between cells and their **environment.**
- Cells detect signals with **Cell Receptors** on their **plasma membrane**. The **signaling molecule (hormone, PG)** binds to the Receptor because its shape is **complementary**. This then instigates a chain of reaction within the cell, leading to a **response**.

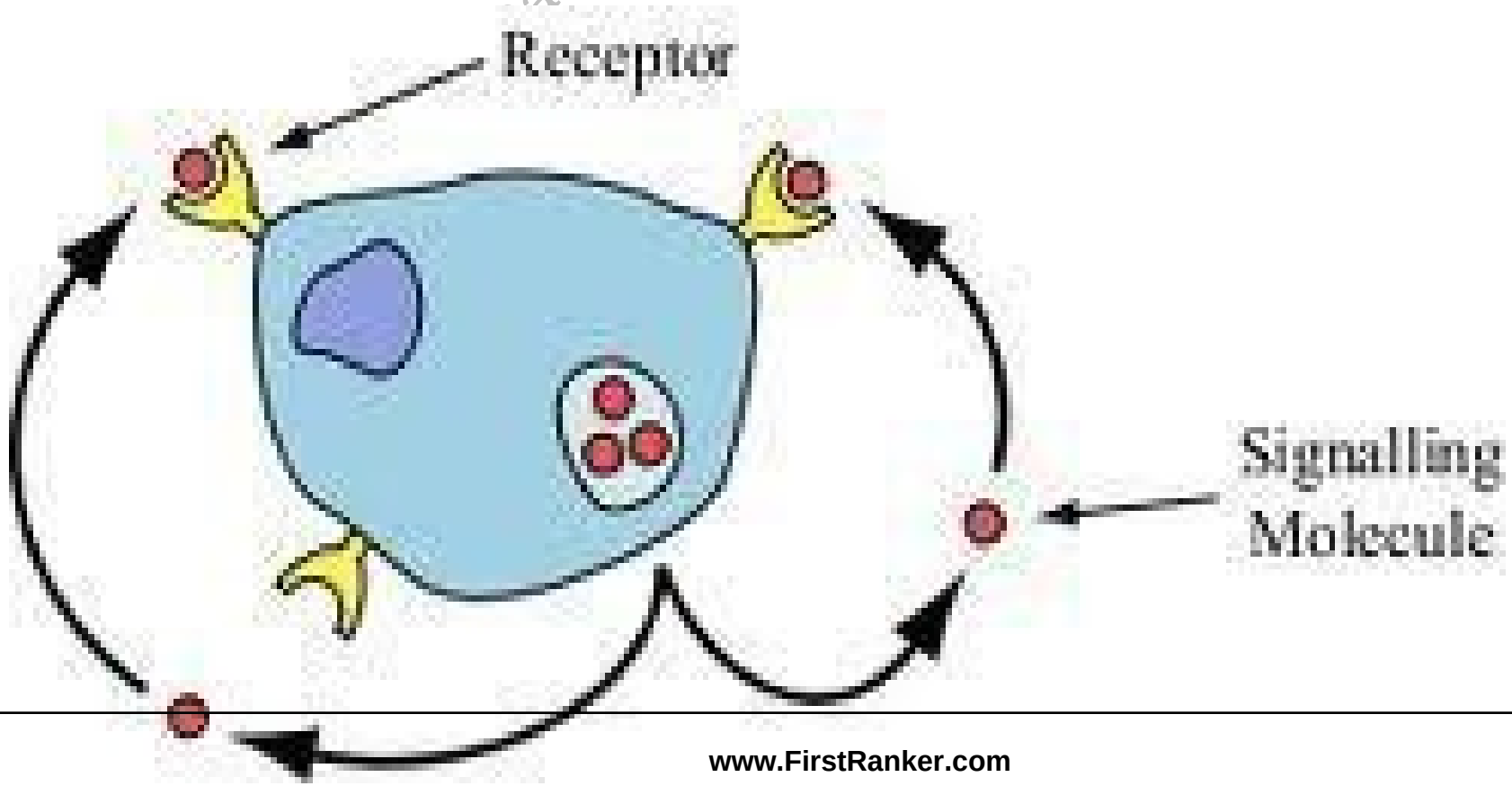
# Types of Cell signaling

**Cell Signaling Pathways** can be categorized based upon the **distance** over which the signaling occurs.

1. Autocrine
2. Paracrine
3. Juxtacrine
4. Endocrine

# Autocrine

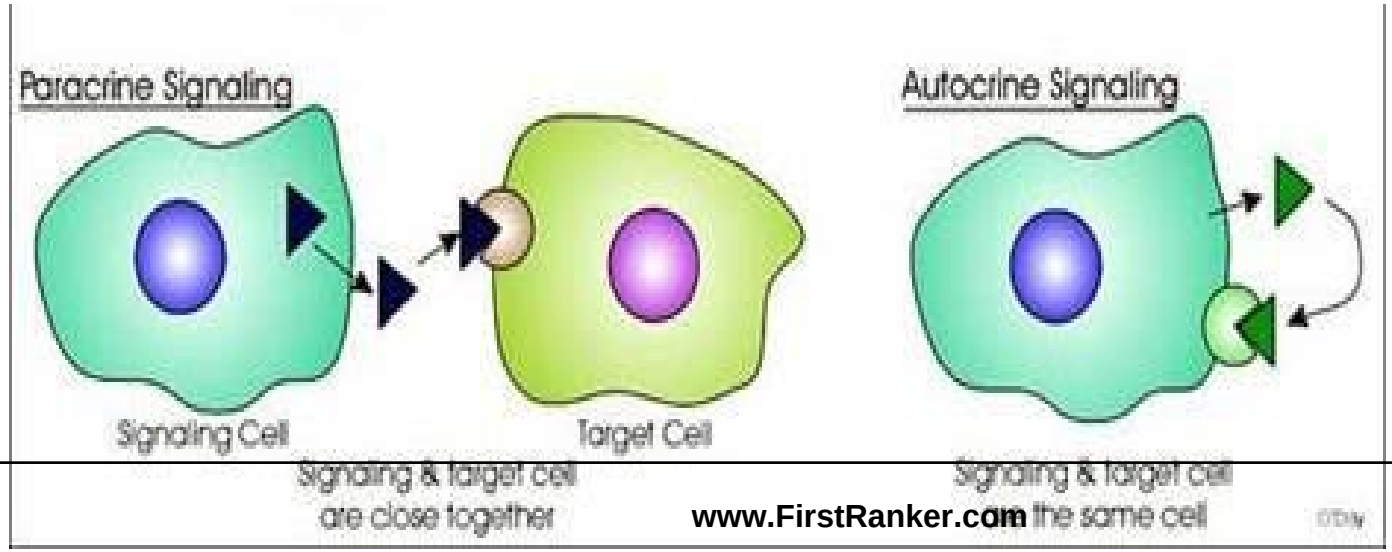
- Is a form of signaling in which a cell secretes a hormone or chemical messenger that binds to autocrine receptors on the same cell, leading to changes in the cells.



# Paracrine

- Is a form of cell signaling in which the target cell is near the signal-releasing cell.
- Proteins(diffusable factors) synthesized by one cell diffuse over short distances to interact with other cell.



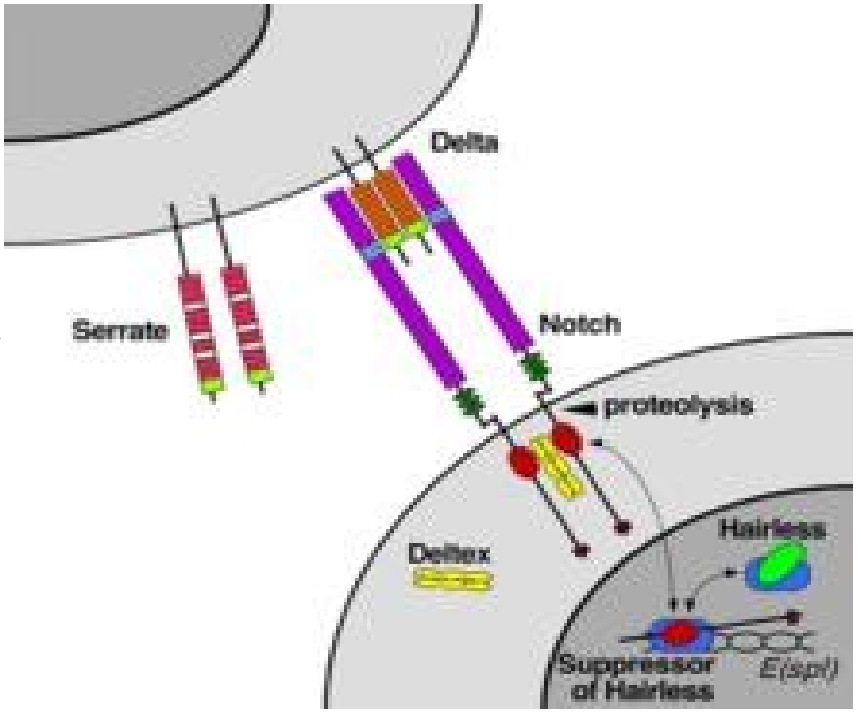


# Juxtacrine Cell signaling



- Involve variety of **non diffusible factors**
- **Occurs between adjacent cells** that possess broad patches of closely opposed plasma membranes linked by transmembrane channels known as **connexons.**
- Juxtacrine signaling ~~requires physical contact~~

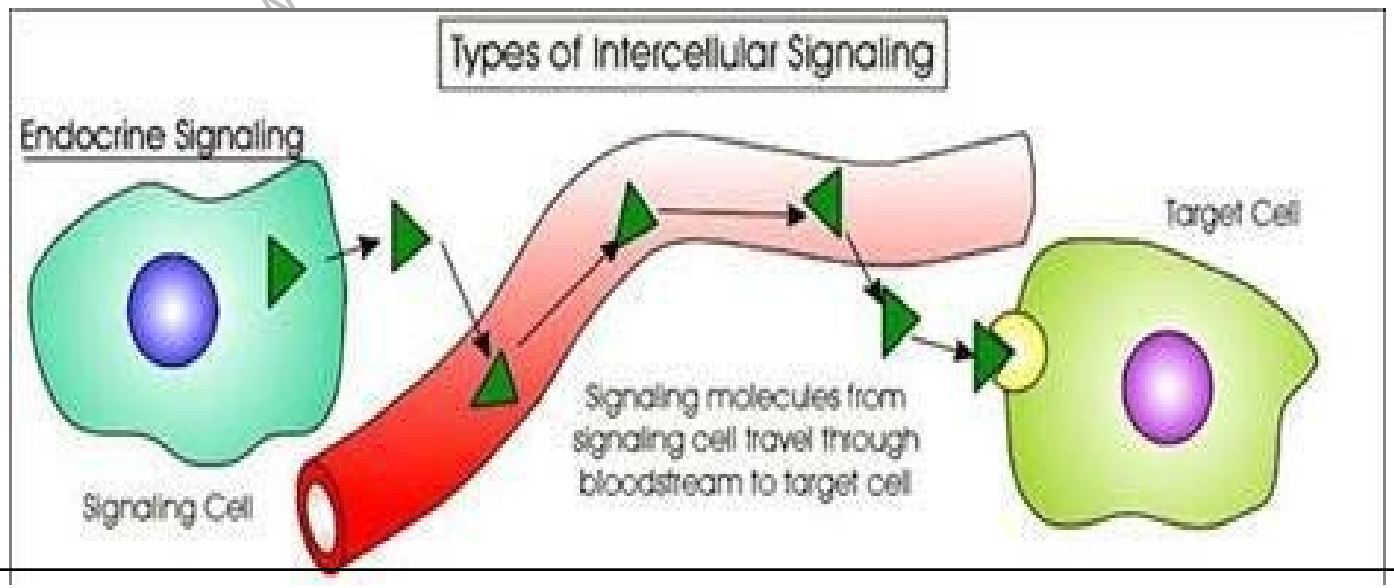
between the two cells involved

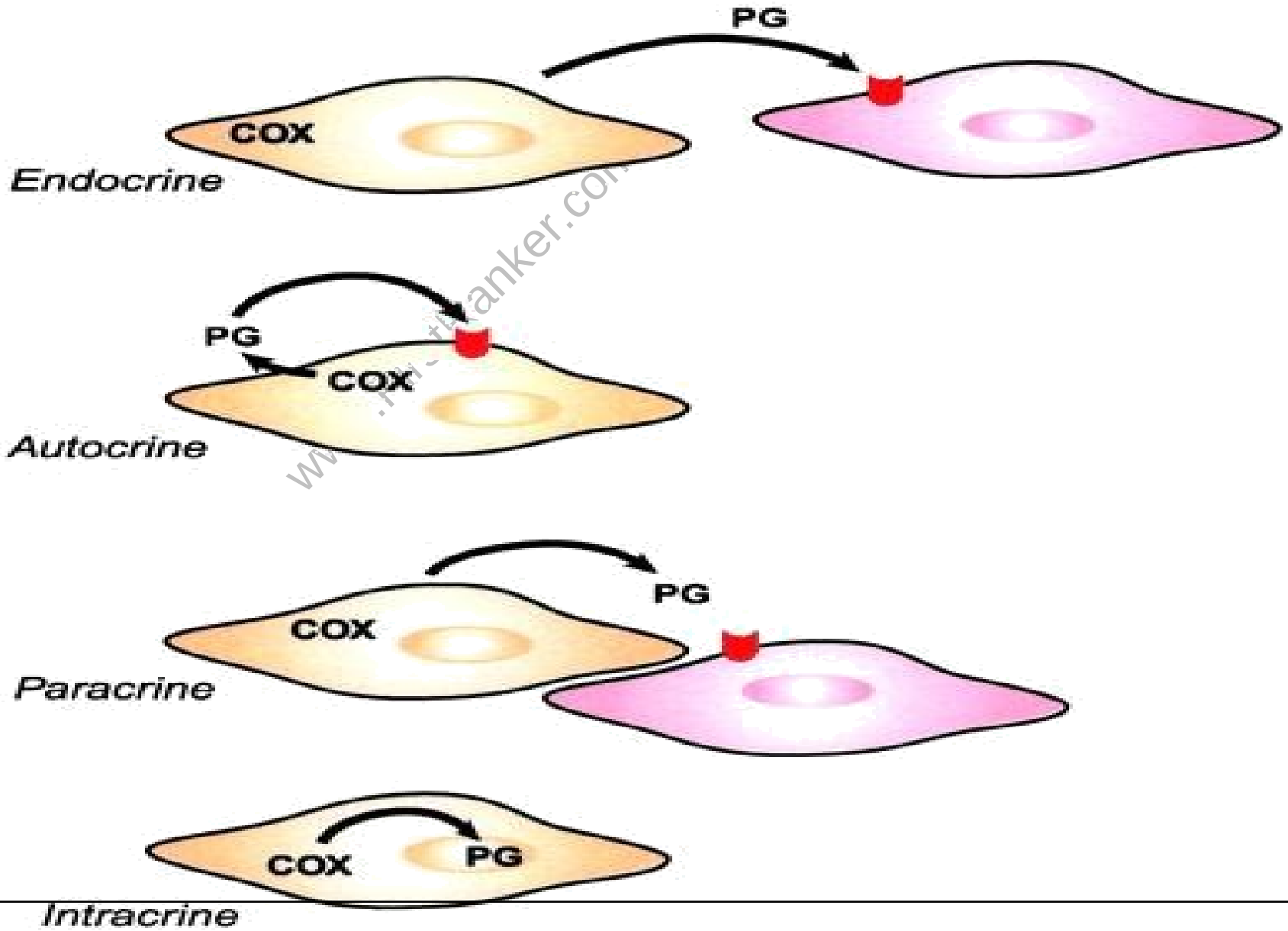


# Endocrine Signaling

- Involves signaling over **large distances**, often where the signaling molecule is transported in the circulatory system






PG
COX
Endocrine
PG
COX
Autocrine
COX
PG
Paracrine
COX
PG
Intracrine

# Paracrine factors or GDFs

Are the **diffusible proteins** responsible for Paracrine signaling.

The four groups of GDFs include:

1. Fibroblast growth factor (FGF)
2. WNT
3. Hedgehog
4. **Tra sfor i g growth factor β fa ilies.**

# FGFs

- Approx. two dozen FGF genes have been identified.
- **FGF proteins** produced by these genes activate **FGFRs.**
- These receptors **activate** various signaling pathways.

**FGFs are particularly important for:**

1. Angiogenesis
2. Axon growth
3. Mesoderm differentiation.
4. FGF8 is important for development of the limbs and parts of the brain.

# WNT Proteins

- There are at least 15 different WNT proteins

  that are involved in developmental pathways.

**WNT proteins are involved in regulating:**

- limb patterning
- Midbrain development
- Some aspects of somite and urogenital differentiation.

# Hedgehog Proteins

- There are three hedgehog genes:

1. Desert
2. Indian
3. sonic hedgehog.



**Sonic hedgehog is involved in a number of developmental events including:**

- limb patterning
- Neural tube induction
- Patterning
- Somite differentiation
- Gut regionalization

# The TGFβ Superfamily

- **The TGFβ superfamily has** over 30 members and includes:

1. The transforming growth **factor βs**
2. The **bone morphogenetic proteins (BMPs)**
3. The activin family
4. The Müllerian inhibiting factor (MIF).



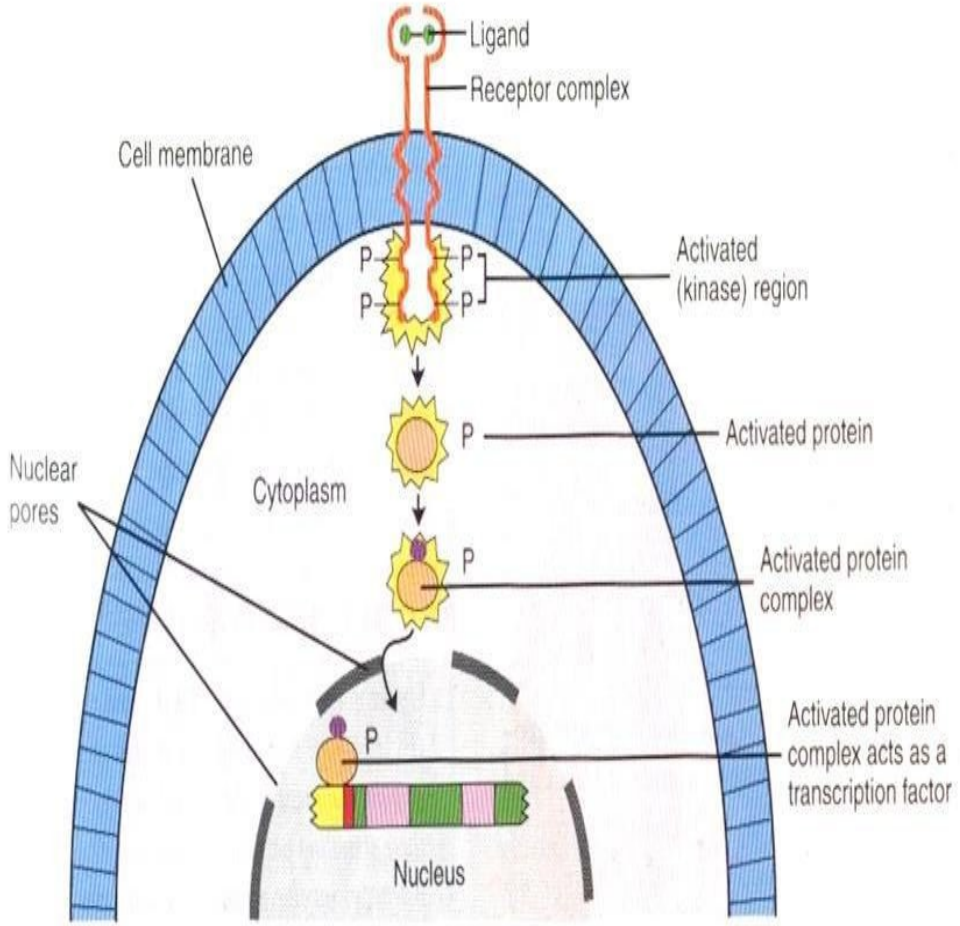
- **The TGFβ members are important for**:
- Extracellular matrix formation
- Epithelial branching that occurs in lung, kidney, and salivary gland development.
- Bone development
- Cell division, apoptosis

# Paracrine Factors

- Act by signal transduction pathways either by activating a pathway directly or by blocking the activity of an inhibitor of a pathway (inhibiting an inhibitor, as is the case with hedgehog signaling).

# Paracrine signaling

- Include a signaling molecule **(the ligand)** and a **receptor.**
- **The receptor** usually spans the cell membrane and is **activated by binding with its specific ligand**.



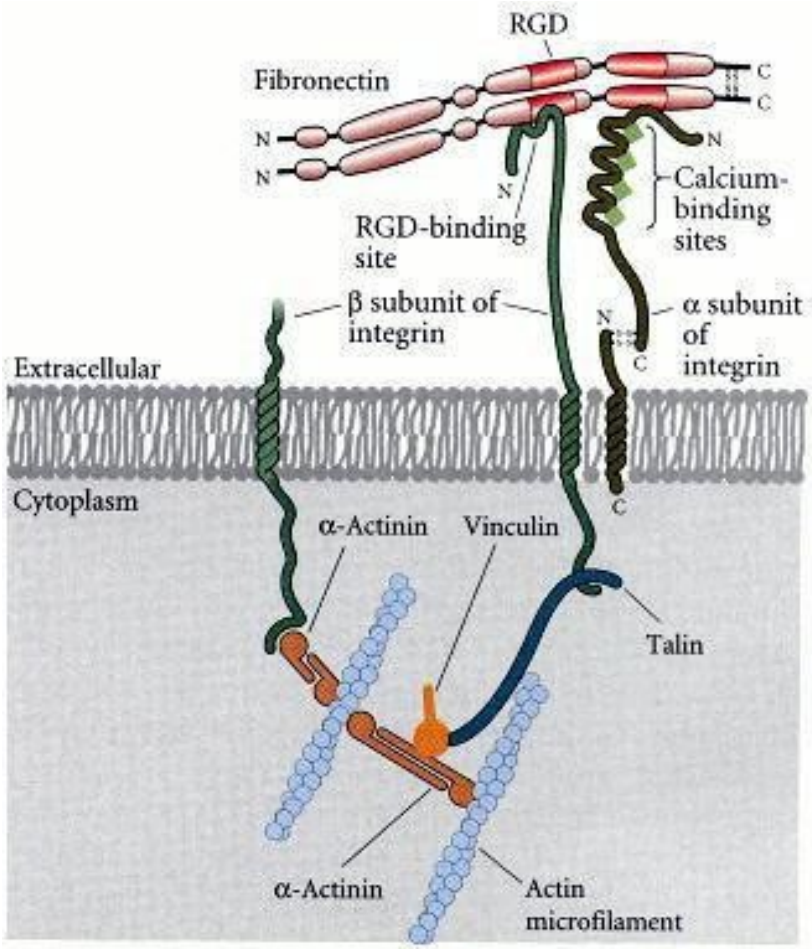
# Juxtacrine Signaling

**Occurs by 3 ways:**

1. **The Notch pathway**
2. **By Ligands**
3. **By direct transmission**

# 2. Ligands

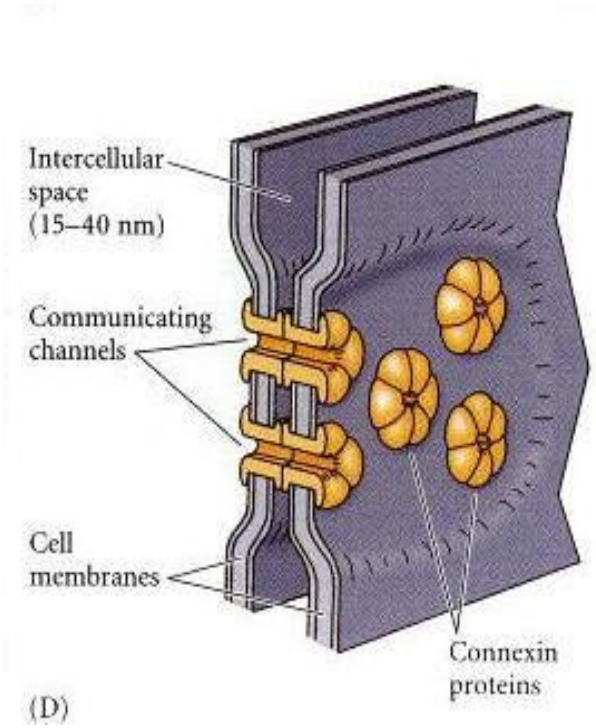
- Are the extracellular matrix molecules (collagen, proteoglycans, fibronectin and laminin) secreted by one cell interact with their receptors on neighboring cells.



# 3. Direct transmission

- of signals from one cell to another through gap junctions (channels) through which small molecules and ions can pass.
- Is important in tightly connected cells like epithelia of the gut and neural tube.





# Conclusion

- Since there is a great amount of **repetition** in the process of signal transduction, therefore **loss of function of a signaling protein** through gene mutation does not necessarily result in abnormal development or death because other members of the gene family may compensate for the loss.

- **Also, there is cross talk between pathways, such that they are intimately interconnected. These connections provide numerous additional sites to regulate signaling.**