Embryology

By: Dr. Saeednia

Embryology
Clinical Relevance & Historical Perspective

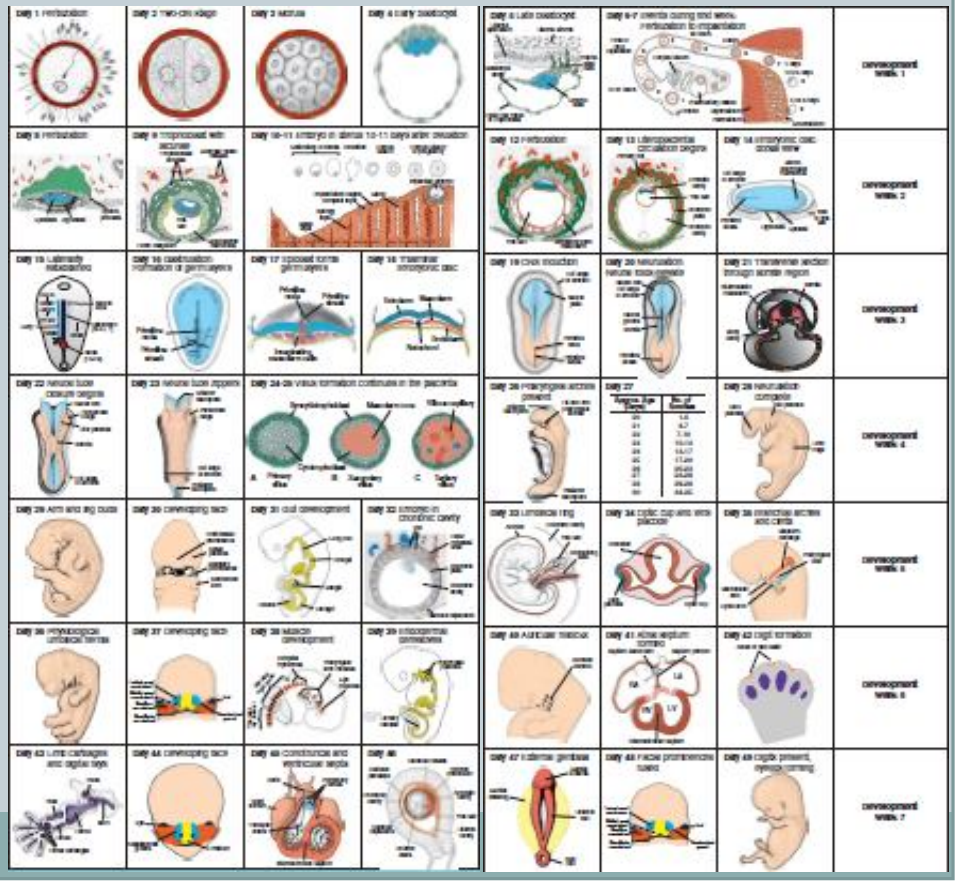
Embryology means:

- *The study of developmental process that convert a single cell to a baby in 9 months*

Embryology compose of:

- Investigations of molecular factor
- Investigations of Cellular factor
- Investigations of structural factors

That are necessary for formation of organism



Embryology
Clinical Relevance & Historical Perspective

Embryology =

- Provide essential knowledge for creating health care strategies for better reproductive outcomes

better understanding of embryology has resulted in:

1. new techniques for prenatal diagnoses & treatments
2. therapeutic procedures to circumvent problems with infertility
3. to prevent birth defects (the leading cause of infant mortality)

History

embryogenesis (organogenesis)=

- The progressing from a single cell to the period of establishing organ primordia
- the first 8 weeks of human development

fetal period=

- a time when differentiation continues
- period from 9th week until birth
- the fetus grows & gains weight

History

Scientific approach in embryology study:

- Early anatomical investigations
- Advances in optical equipment and dissection techniques
- Comparative and evolutionary studies among species
- Comparative studies between offspring with birth defects & organisms with normal developmental patterns

Teratology: the study of origin and embryological reason of maternal defects

History

20th century

Formation of Experimental embryology

observations of embryos from tunicates that contained pigmented cell

living cells staining & follow their fates using vital dyes

History

1960s, radioactive labels & autoradiographic techniques

- **creation of chick-quail chimeras (**is a single organism composed of cells from different zygotes)
- quail cells with unique pattern of heterochromatin were grafted into chick embryos

  at early stages of development
- Histological observations & determination of the quail cells fates
- The production of antibodies specific to quail cell antigens
- valu able information about the origins of different organs & tissues

History

- Grafting experiments form data from **Tissues signaling:**
- **Such as:**

1. ***the primitive node grafting***
   a second body axis induction

2. ***posterior axial border grafting*** **(zone of polarizing activity (ZPA))**
   digits duplication in recipient limb

Signaling molecule:
(sonic hedgehog (SHH))

History

Teratology science formation in 1961

- **thalidomide**

Anti nausea & sedative
High range of birth defects
limbs abnormalities
Amelia or phocomelia

- W. Lenz and W. McBride

The embryo was vulnerable to **maternal factors that crossed the placenta**

- **Using animal model for effects of :**

Environmental factors
Drugs
gens

History in Experimental embryology

- **molecular approaches add to :**
  Study normal & abnormal development

cells identifying instruments:

- reporter genes,
- fluorescent probes
- other marking techniques

ability to map cell fates

techniques for altering gene expression

1. knockout
2. knock-in
3. antisense technologies (presents an opportunity to manipulate gene expression within the cells to treat various diseases, and acts as a powerful tool for studying gene function)

Molecular Regulation & Signaling

Molecular biology=

opened the doors to new ways to study embryology and to enhance our understanding of normal and abnormal development

- Sequencing the human genome
- 23000 genes (primary predicted 100,000)
- the one-gene–one protein hypothesis disproved

Gene expression is regulated at several levels:

1. different genes may be transcribed
2. DNA transcribed from a gene may be selectively processed to regulate which RNAs reach the cytoplasm to become mRNAs
3. mRNAs may be selectively translated
4. proteins made from the mRNAs may be differentially modified

GENE TRANSCRIPTION

- Genes are contained in a complex of DNA & proteins (mostly histones) called **chromatin**
- **Nucleosome form** the basic unit of chromatin structure

Nucleosome :

- octamer of **histone proteins**
- 140 DNA bp

- Nucleosome clusters by **linker DNA & H1 histones**

- **Heterochromatin (inactive chromatin)**
- **Euchromatin (active chromatin)**

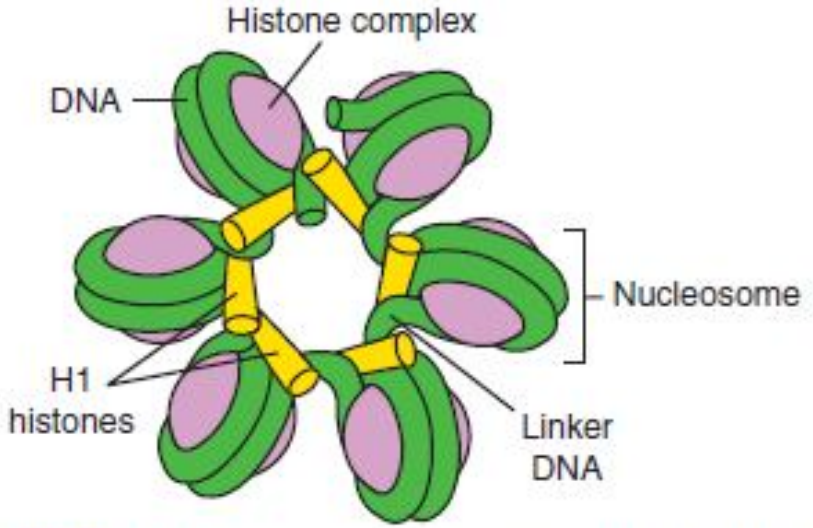


Figure 1.1 Drawing showing nucleosomes that form the basic unit of chromatin. Each nucleosome consists of an octamer of histone proteins and approximately 140 base pairs of DNA. Nucleosomes are joined into clusters by linker DNA and other histone proteins.

Gene structure

- **exons,** translated into proteins,
- **introns,** between exons & are not translated into proteins

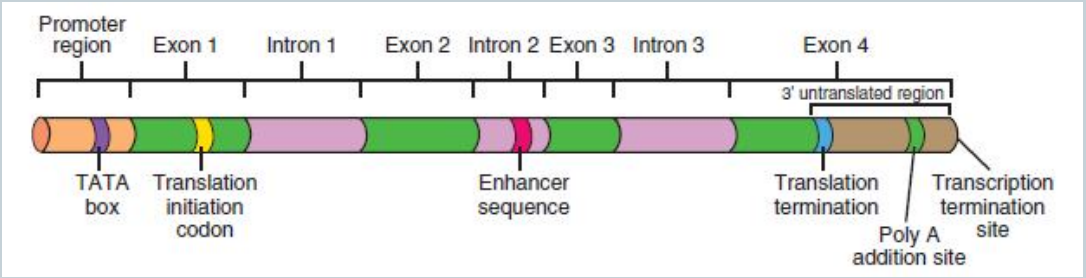
a typical gene includes:

- a **promoter region**

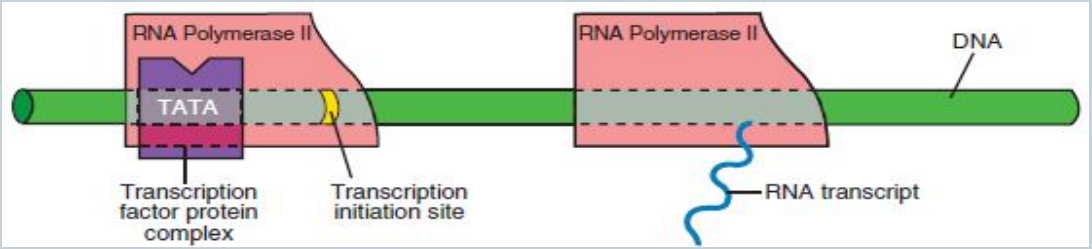
that RNA polymerase binding site (TATA box)

- a **transcription initiation site**
- **a translation initiation site**
- a **translation termination codon**
- **a 3′ untranslated region**

(the poly A addition site)



- Transcription factors
- Enhancers
- silencers



DNA Methylation

DNA methylation=

1. **Represses Transcription**
2. **X chromosome inactivation**
3. **genomic imprinting**

- 40 to 60 human genes are imprinted
- methylation patterns are established during spermatogenesis & Oogenesis

Methylation silences DNA by:

- inhibiting binding of transcription factors
- Altering histone binding & stabilization of nucleosomes and tightly coiled

The other gen expression regulators:

- **nuclear RNA (nRNA) or *premessenger RNA (***The initial transcript***)**

introns that are removed **(spliced out) in** movement from the nucleus to the cytoplasm

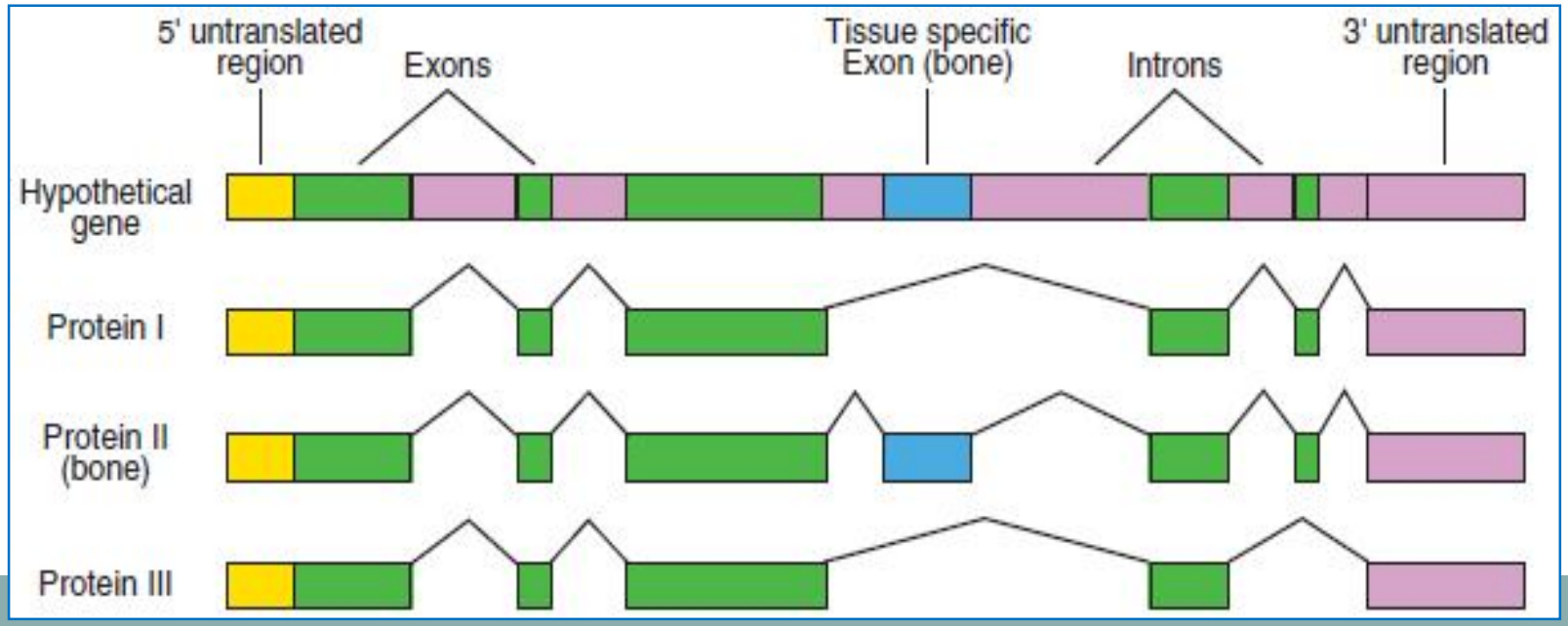
- **alternative splicing (**Cells produce different proteins from a single gene)

spliceosomes

- **small nuclear RNAs (snRNAs)**

&

- **proteins that recognize specific** splice sites at the 5′ or the 3′ ends of the nRNA



splicing isoforms (also called splice variants or **alternative splice forms)**

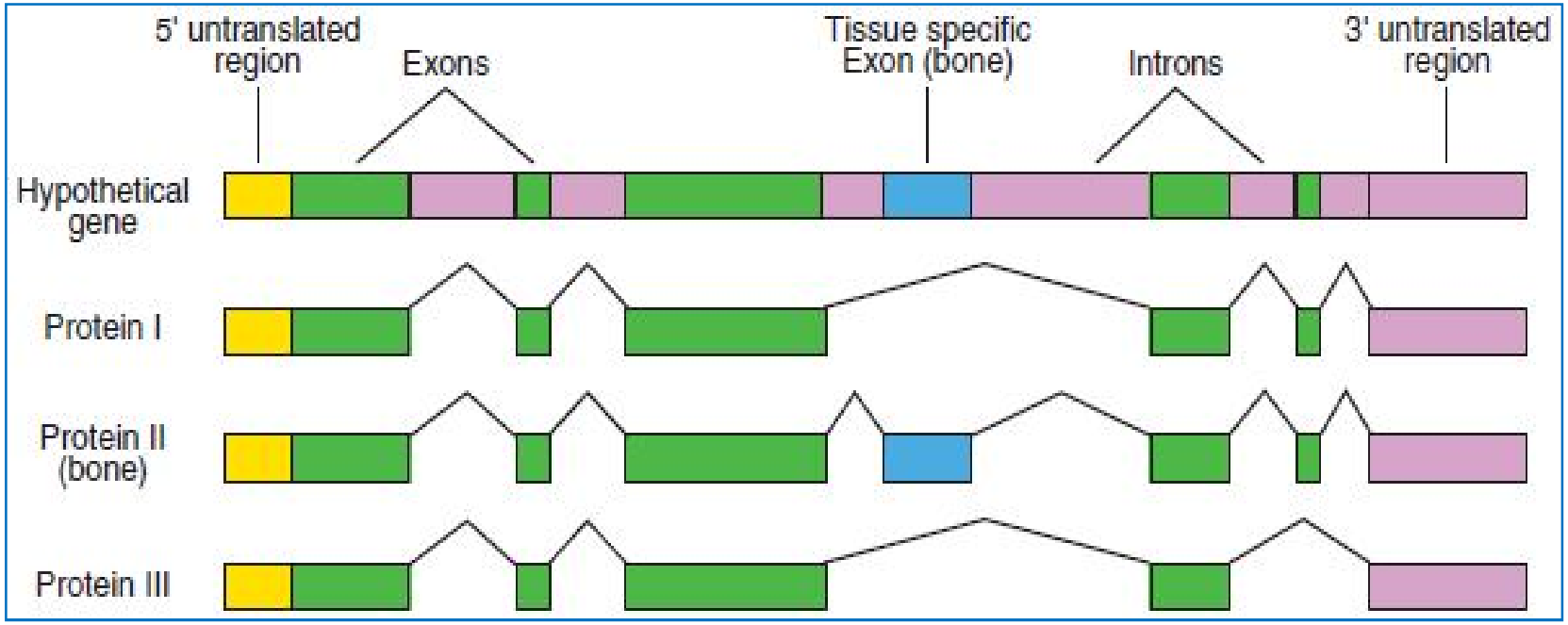
opportunity for different cells to use the same gene to make proteins specific for that cell type.

isoforms of the *WT1 gene* have different functions in gonadal versus kidney development

post-translational modifications (affect its function)

cleavage or phosphorylation to become active

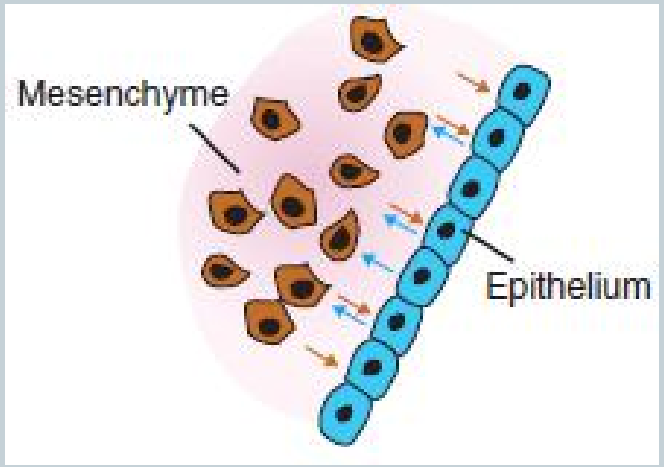
only 23,000 genes exist, but number of proteins five times more



Induction & Organ Formation

Induction composed of :

- **Inducer** (signal)
- **responder**
- **Competence & competence factor**



inductive interactions consist of :

➢ **epithelial– mesenchymal Interactions**

Epithelial cells (attach to each other in tubes or sheets form)
mesenchymal cells (fibroblastic like that dispersed in ECM)

e.g.

- gut endoderm and surrounding mesenchyme (liver & pancreas)
- limb mesenchyme with overlying ectoderm (epithelium limb outgrowth & differentiation)
- endoderm of the ureteric bud and mesenchyme from the metanephric blastema nephrons in the kidney

➢ **Inductive interactions between two epithelium**

e.g.

- lens formation by epithelium of the optic cup

Point:

crosstalk between the two tissues or cell is essential for differentiation

Cell Signaling

- **Cell-to-cell signaling is essential for =**

- induction
- conference of competency to respond
- crosstalk between inducing and responding cells

- **paracrine interactions (the effect of manufactured protein in peripheral cells / paracrine factors)**

- **Juxtacrine interactions (not related to protein)**

Paracrine signaling

- **paracrine interactions**

signal transduction pathways consist of :

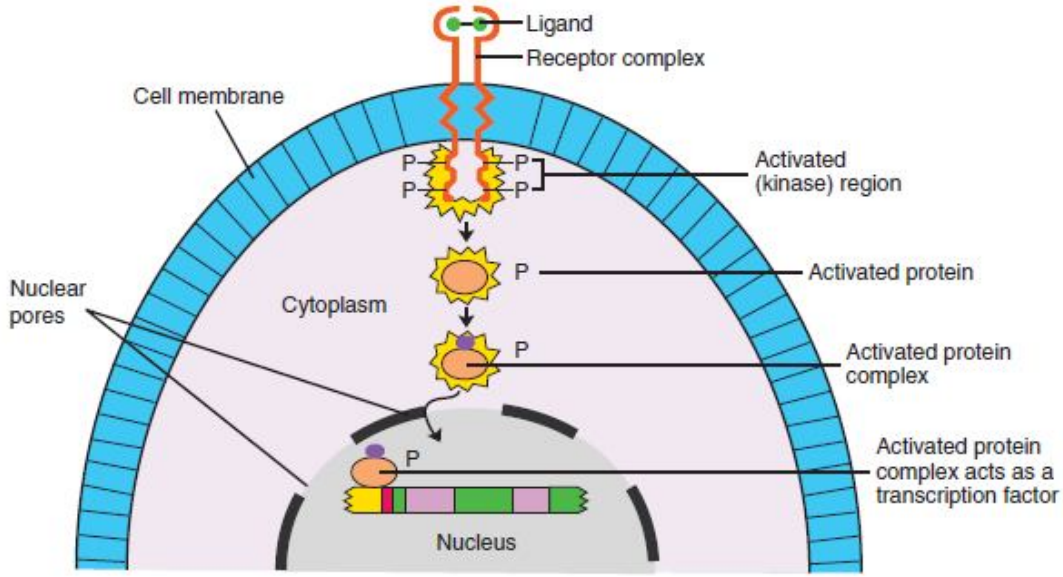
- **signaling molecule (the ligand)**
- **receptor**

- **The receptor parts:**

extracellular Domain , a transmembrane domain, a cytoplasmic domain

- Ligand-receptor complex :
- 3D change in receptor
- cytoplasmic domain activation
- Enzymatic activity
- a **kinase activation**
- By ATP consumption
- proteins phosphorylation cascade
- **transcription factor activation**
- **Activate or suppress gen expression**

hedgehog signaling



Juxtacrine Signaling

- **No diffusible factors (diffusible protein)**
- **Have 3 pathway:**

(1)

A protein on one cell surface interacts with a receptor on an adjacent cell

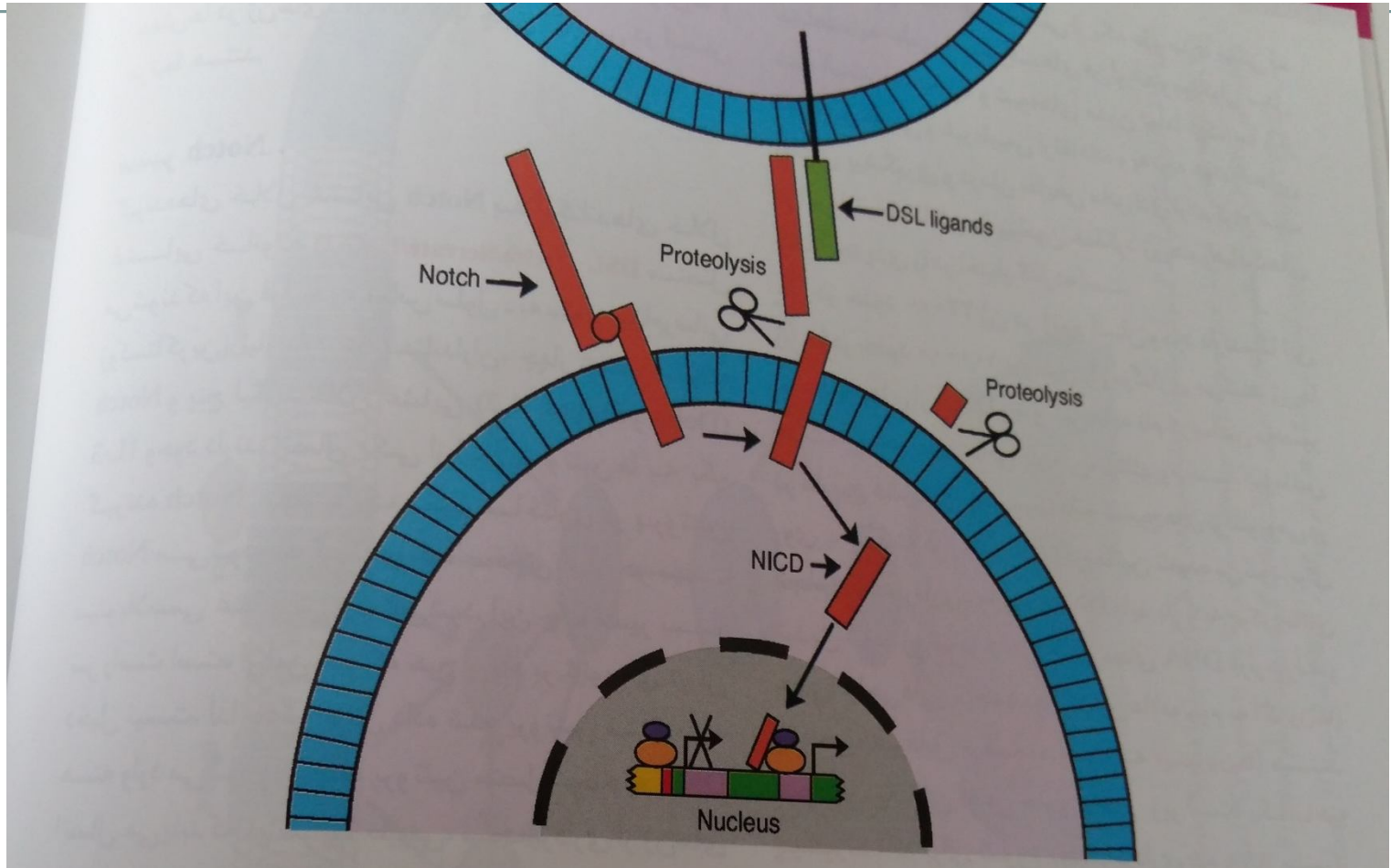
- **Notch pathway**

  Notch receptor protein (receptor)

  Delta, Serrate, or Jagged proteins (ligand)

In:

- neuronal differentiation
- blood vessel specification
- somite segmentation



شکل ۹-۱. نحوه پیغام‌رسانی از طریق مسیر Notch. گیرنده‌های Notch واقع بر یک سلول، به یک لیگاند از خانواده (DSL Jagged یا Serrate) متصل می‌شوند که بر روی یک سلول مجاور قرار دارند (پیغام‌رسانی ژوکستا کرین) و این اندرکنش گیرنده لیگاند، یک آنزیم پروتئولیتیک را فعال می‌سازد که پروتئین Notch را برش می‌دهد تا NEXT (بخش خارج سلولی Notch متصل به غشا و فعال شده) را تولید کند. سپس NEXT را یک آنزیم سکرتاز داخل سلولی برش می‌دهد که به آزادسازی NICD (حوزه داخل سلولی Notch) می‌انجامد. NICD بخش پیغام‌رسان فعال گیرنده Notch اولیه است که مستقیماً به هسته می‌رود و در این جا به سرکوب‌کننده‌های نسخه‌برداری متصل می‌شود و فعالیت مهاری آنها را از روی ژن‌های هدف پایین دستی مسیر Notch برمی‌دارد.

Juxtacrine Signaling

(2)

- Ligands in ECM (collagen IV – laminin)
- Receptor on surrounding cell surface (integrin)

ECM contains large molecules

Collagen

proteoglycans (chondroitin sulfates, hyaluronic acid, etc.)

Glycoproteins (fibronectin and laminin)

receptors functions:

- Integrin **integrate** matrix molecules = facilitate migration of cells in ECM
- integrin **induce gene expression** and **regulate differentiation** (e.g. chondrocyte that must be linked to the matrix to form cartilage)

Juxtacrine Signaling

(3)

- signals transmission by **gap junctions**

  junctions occur as channels between cells through

  Channel = connexin proteins

Paracrine Signaling Factors

- **growth and differentiation factors (GDFs) consist of The 4 groups :**

1. Fibroblast growth factor (FGF) / FGF Receptor

functions: angiogenesis, axon growth, and mesoderm differentiation

2. WNT

related to the segment polarity gene , *wingless*

receptors =frizzled family proteins)

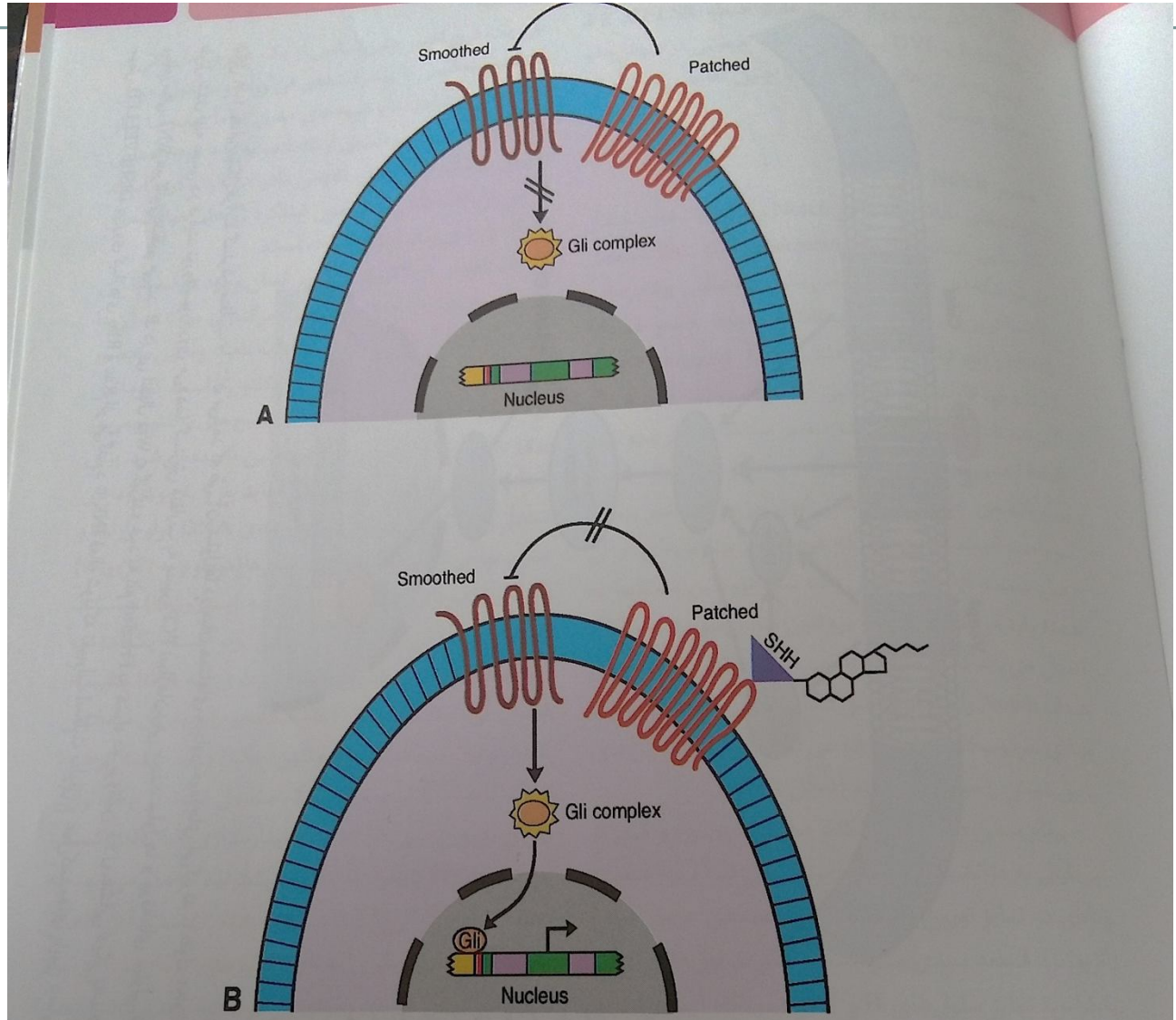
functions: regulating limb patterning, midbrain development, somite & urogenital differentiation

3. Hedgehog

3hedgehog genes = ligand = (Desert, Indian, sonichedgehog)

hedgehog family receptor = Patched

functions: limb patterning, neural tube induction and patterning, somite differentiation, gut regionalization



شکل ۷-۱. مسیر پیغام‌رسانی SHH. **A.** این شکل مهار Smo را توسط Ptc نشان می‌دهد که فعال‌سازی پروتئین‌های GLi را متوقف می‌کند. این پروتئین‌ها در شرایط طبیعی، پیغام SHH را منتقل می‌کنند. **B.** این شکل اتصال SHH را به گیرنده‌اش (Ptc) نشان می‌دهد که مهار Smo را برطرف می‌کند. فعال‌سازی Smo فاکتورهای نسخه‌برداری GLI را افزایش می‌دهد که به DNA متصل می‌شوند و ژن‌های عمل‌کننده را در مسیر SHH تنظیم می‌کنند.

Paracrine Signaling Factors

4. Transforming growth factor-b (TGF-β)

TGF- β family consist of :

BMPs family
activin family
the Müllerian inhibiting factor (MIF, anti-Müllerian hormone)

Functions:

TGF- β formation of extracellular matrix & epithelial branching that occurs in lung, kidney, & salivary gland development

BMP family induces bone formation, regulating cell division, cell death (apoptosis), & cell migration

Paracrine Signaling Factors

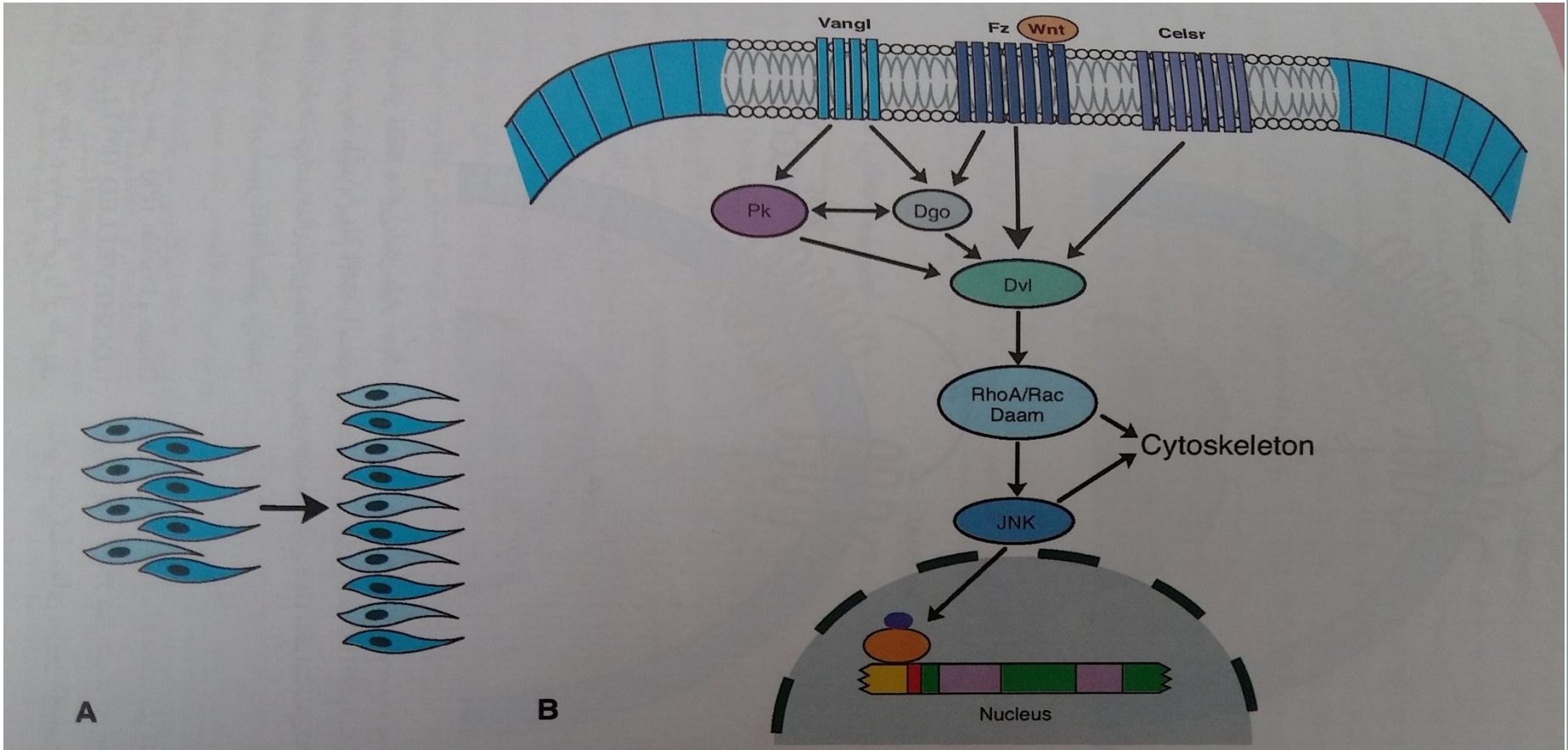
- **neurotransmitters**

Ligand = Serotonin

Receptors = G protein–coupled

Functions : cell proliferation & migration, establishing laterality, gastrulation, heart development

Norepinephrine in apoptosis (programmed cell death) in the interdigital spaces and in other cell types



شکل ۸-۱. A. این شکل فرآیند گسترش متقارب را نشان می‌دهد که طی آن، سلول‌ها در میان همتاهای مجاور خود جای می‌گیرند تا طول محور بلند یک بافت افزایش یابد (نظیر آن چه در جریان طویل شدن لوله عصبی در فرآیند نورولاسیون روی می‌دهد). گسترش متقارب به مسیر PCP (سازمان‌دهی مجدد سلول‌ها و ورقه‌های سلولی در صفحه یک بافت) بستگی دارد که آن را مسیر پیغام‌رسانی WNT غیرکانونی تنظیم می‌کند. **B.** در پی اتصال Wnt به گیرنده خود به نام Frizzled به همراه دو پروتئین خلال غشایی دیگر به نام Celsr و Vangl، DISHEVELLED فعال می‌شود. سپس DISHEVELLED بر روی کینازهای Rho و Rac اثر می‌گذارد تا JNK فعال شود که تغییرات اسکلت سلولی و عمل‌کننده‌های پایین دستی (ازجمله فاکتورهای نسخه‌برداری) را تنظیم نماید.