Genetics

Modified no. 16

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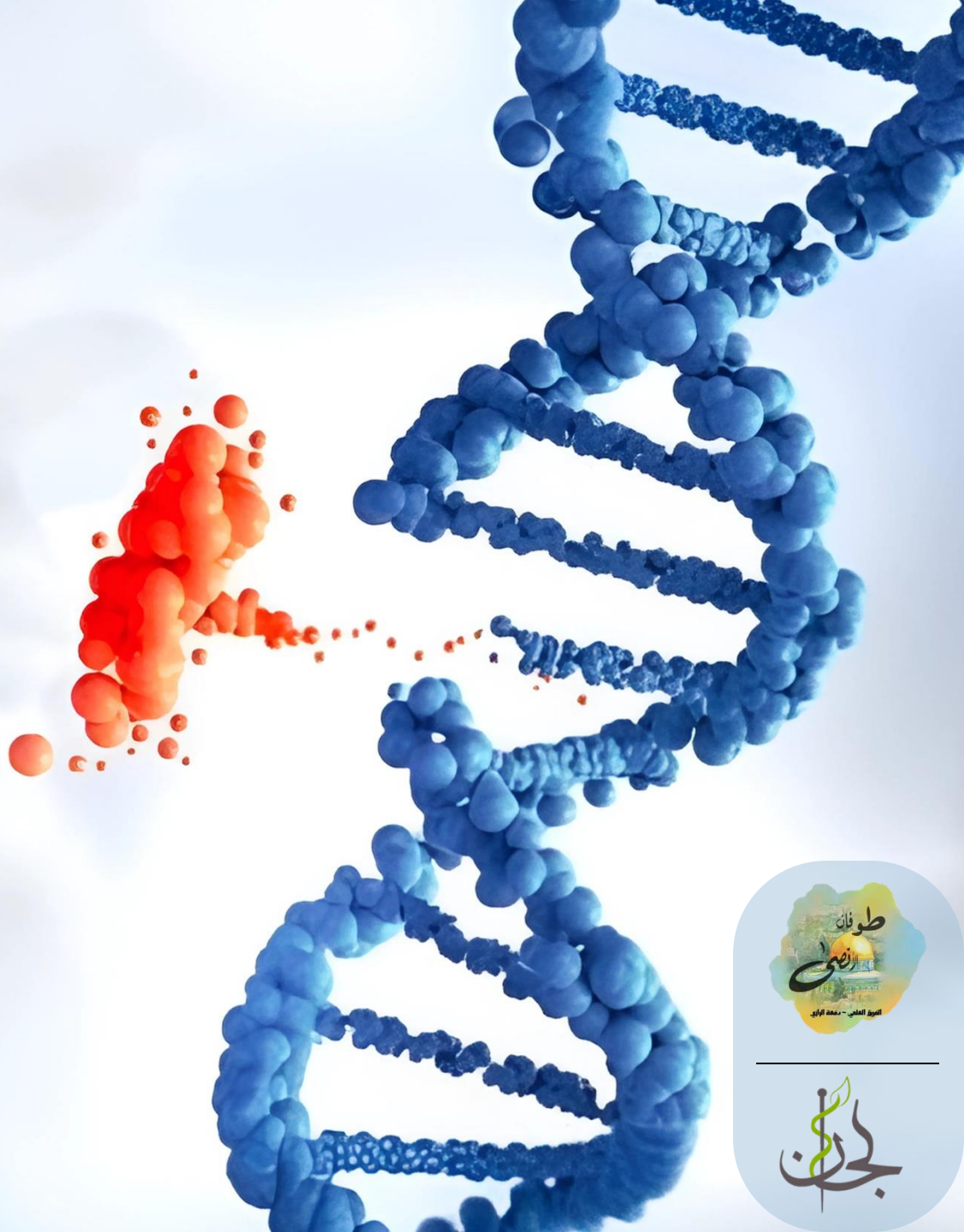


Developmental Genetics

We will discuss **Genes** that are **activated during embryonic development** and **then** After the development is completed, these genes are subsequently **deactivated**.

Color code
Slides
Doctor
Additional info
Important

Basic Concepts

- A single fertilized egg (A zygote) divides and grows to form different cell types, tissues, and organs, all of which are arranged in a species-specific body plan (i.e., the arrangement and pattern of body parts).
- Many of the instructions necessary for normal development are encoded by an animal's genes (which determine body plan).

- Approximately 2% to 3% of babies are born with a recognizable birth defect.
- Some birth defects are caused by mutations in genes encoding elements in pathways that control development. These pathways are highly conserved among animal species. (if there is no conservation for developmental genes, they will extinct)

Basic Concepts

- For ethical and technical reasons, it is difficult to study early developmental events in human embryos (Studying embryonic development requires the monthly extraction and dissection of embryos, a process that inevitably involves sacrificing the embryos, which is not ethical, additionally , human development take long period about 9 months to be completed.

→ a variety of nonhuman **model organisms** are used to facilitate the study of development.

- This approach is feasible because the major elements (genes and pathways) that control animal development are conserved across a wide range of species and body plans.
- In addition, many regulatory switches and signaling pathways are used repeatedly during development to control various patterning and differentiation events.

TABLE 10-1 Animal Models of Human Development

ORGANISM	GENERATION TIME*	ADVANTAGES	DISADVANTAGES
Caenorhabditis elegans (roundworm)	9 days	Fate of every cell known Genome well characterized Easy to breed and maintain	Alternative body plan compared to vertebrates Tissues cannot be cultured
Drosophila melanogaster (fruit fly)	10 days	Easy to breed Large populations Vast database of mutants Feasible and affordable to do large screens	Alternative body plan compared to vertebrates Must be stored live; cannot be frozen Pathology often different compared to humans
Danio rerio (zebrafish)	3 months	Transparent embryo Easy to maintain Large populations Feasible and affordable to do large screens	Targeted gene modification difficult
Xenopus laevis (frog)	12 months	Transparent embryo is large and easy to manipulate	Tetraploid genome makes genetic experiments difficult
Gallus gallus (chicken)	5 months	Easy to observe and manipulate embryo	Genetic experiments difficult
Mus musculus (mouse)	2 months	Pathology similar to humans Excellent tools for phenotypic characterization Targeted gene modification straightforward Fully annotated genome available	Relatively expensive to maintain Manipulation of embryo is challenging
Papio hamadryas (baboon)	60 months	Pathology and physiology similar to that of humans	Very expensive to maintain Small populations Long generation time Strong ethical concerns with use of Primates لأنها معرضة للانقراض

*Generation time is defined as the age at which the organism is first capable of reproduction.

Table shows many organisms we study their developmental genes and look for similarities with human genome.
Generation time column shows when the organism is capable of reproduction, (Generation time refers to the average interval between the birth of an individual and the birth of its offspring) ChatGPT.

Generation time is important,For example you need 60 months to study one generation of baboon, and 120 months to study two generations.
Frog has transparent embryo that easy to manipulate but its genetic experiments is difficult like chicken.
Whereas mouse is the best model similar to human pathology and its genes can be easily modofied but is expensive.

Overview of Major Processes in Embryonic Development

- Embryonic development involves the processes of pattern formation, axis specification, and organogenesis.

1. Pattern formation describes a series of steps in which differentiated cells are arranged spatially to form tissues and organs.
2. Axis specification involves the definition of the major axes of the body: ventral/dorsal, anterior/posterior, medial/lateral, and left/right. You studied in anatomy
3. As the axes are specified, the formation of organs and limbs (organogenesis) begins.

- Each of these processes is controlled by a series of proteins that provide signals and form structures necessary for normal development of the embryo.

GENETIC MEDIATORS OF DEVELOPMENT: THE MOLECULAR TOOLBOX

Genetic mediators include:

- The genes required for normal development encode many different products, including [1]signaling molecules and their receptors, [2]DNA transcription factors, [3]components of the extracellular matrix, [4]enzymes, [5]transport systems, and other proteins.

- Each of these genetic mediators is expressed in combinations of spatially and temporally (مکان و زمان) overlapping patterns that control different developmental processes. Highly organized process

- Mutations in the genes mediating development are a common cause of human birth defects.

TABLE 10.2 ■ Genes That Cause Human Birth Defects

Gene	Type of protein	Syndrome	Birth defects
BOR1	Transcription factor	Branchio-oto-renal	External ear anomalies, hearing loss, kidney defect
COL2A1	Extracellular matrix protein	Stickler	Skeletal dysplasia, cleft palate, nearsightedness
EMX2	Transcription factor	Schizencephaly	Clefting of the cerebral cortex
EvC	Transcription factor	Ellis-van Creveld	Skeletal dysplasia, extra digits, heart defects
GLI3	Transcription factor	Greig	Premature fusion of the cranial sutures, extra digits
GLI3	Transcription factor	Pallister-Hall	Hypothalamic hamartomas, extra digits
GLI3	Transcription factor	Polydactyly type A	Extra posterior digits
HOXA13	Transcription factor	Hand-foot-genital	Hypoplasia of the first digits, kidney and genital defects
HOXD13	Transcription factor	Synpolydactyly	Extra digits that are often fused with other digits
IHH	Signaling molecule	Brachydactyly A1	Short fingers and toes
IRF6	Transcription factor	van der Woude	Cleft lip/palate with lip pits
IRF6	Transcription factor	Popliteal pterygium	Cleft lip/palate, webbing across joints
KIT	Receptor molecule	Piebaldism	Hypopigmented patches of skin
LMX1B	Transcription factor	Nail-patella	Anomalies of bones, kidneys, fingernails
MITF	Transcription factor	Waardenburg	Hypopigmentation, hearing impairment
MSX1	Transcription factor	—	Cleft lip/palate, missing teeth
NOG	Extracellular protein	Multiple synostosis	Abnormal fusion of bones, hearing loss
TP63	Transcription factor	Ectrodactyly/ectodermal dysplasia	Limb, teeth, hair defects, skin, cleft palate
PAX2	Transcription factor	—	Kidney and optic nerve defects
PAX3	Transcription factor	Waardenburg	Hypopigmentation, hearing impairment
PAX6	Transcription factor	Aniridia	Hypoplasia or aplasia of the irides
PAX9	Transcription factor	Oligodontia	Missing teeth
ROR2	Receptor molecule	Robinow	Short forearms and digits
RIEG1	Transcription factor	Rieger	Defects of teeth, eyes, and umbilicus
SALL1	Transcription factor	Townes-Brocks	Anal, kidney, limb, and ear defects
SALL4	Transcription factor	Okihiro	Limb, heart, and ocular defects
SHH	Signaling molecule	Holoprosencephaly	Lack of midline cleavage of the brain
SOX9	Transcription factor	Campomelic dysplasia	Skeletal defects, sex reversal
SOX10	Transcription factor	Hirschsprung	Bowel hypomotility
TBX3	Transcription factor	Ulnar-mammary	Posterior upper limb anomalies, breast and genital anomalies
TBX4	Transcription factor	Small patella	Small or absent patella
TBX5	Transcription factor	Holt-Oram	Anterior upper limb anomalies, heart defects
TBX22	Transcription factor	—	Ankyloglossia, cleft palate
TCOF1	Transcription factor	Treacher Collins	Mid-face hypoplasia, small jaw, external ear defects
WT1	Transcription factor	Denys-Drash	Kidney defects, sex reversal
DHCR7	Catalytic enzyme	Smith-Lemli-Optiz	Mental retardation, syndactyly, multiple organ defects

Don't memorize this, it just shows you genetic mutations and their result defects.

A. Paracrine Signaling Molecules

- Interactions between neighboring cells are usually mediated by proteins that can diffuse across small distances to induce a response.
- These molecules are often called paracrine factors because they are **secreted into the space surrounding a cell** (unlike hormones, which are secreted into the bloodstream).

- There are four major families of paracrine signaling molecules:

When there is a defect in these genes, it leads to a deficiency in signaling molecules, which results in an inadequate cellular response and consequently causes developmental defects due to abnormal cell to cell communication

(1) the fibroblast growth factor {FGF) family;

(2) the Hedgehog family;

(3) the Wingless {Wnt) family; and

(4) the Transforming Growth Factor β (TGF-β) family.

B. DNA Transcription Factors

- Genes encoding proteins that turn on (activate) or turn off (repress) other genes are called transcription factors. Transcription factors commonly do not activate or repress only a single target. So they work on multiple targets rather than one
- There are many different families of transcription factors, each of which regulates the transcription of specific genes.
- The same transcription factor is often used in different developmental pathways.

→ disorders caused by mutations in genes encoding transcription factors are often pleiotropic. It means that single mutation can induce multiple phenotypes

- Examples include homeobox-containing genes such as the HOX, PAX, EMX, and MSX families; high-mobility group (HMG)-box-containing genes such as the SOX family; and the T -box family.

C. Extracellular Matrix Proteins

- EMPs are secreted macromolecules that serve as a dynamic scaffolding (Fillings) for tissues and organs. They are also active mediators of development.
- These molecules include collagens, fibrillins, proteoglycans, and large glycoproteins such as fibronectin, laminin, and tenascin.

- For example, the proteins encoded by fibrillin-1 and elastin coordinate microfibril assembly in the extracellular matrix.

→ Mutations in these two genes result in Marfan syndrome and supravalvular aortic stenosis, respectively. Both of these conditions are characterized by abnormalities of the heart and/or large blood vessels.

1.PATTERN FORMATION

- The process by which ordered spatial arrangements of differentiated cells create tissues and organs is called pattern formation.

- The general pattern of the animal body plan is laid down during embryogenesis. This leads to the formation of semiautonomous regions of the embryo, in which the process of pattern formation is repeated to form organs and appendages.

- Regional specification takes place in several steps:

(1) definition of the cells of a region,

(2) establishment of signaling centers that provide positional information, and

(3) differentiation of cells within a region in response to additional cues.

- For example, cells in the developing vertebrate upper limb differentiate into many cell types, including muscle (myocytes), cartilage (chondrocytes), and bone cells (osteocytes).

→ these cells must also be arranged in a temporal-spatial pattern that creates functional muscle and bone.

- Additional information is required to determine whether a bone becomes an ulna or a humerus. How do particular structures develop in specific places? How do cells acquire information about their relative positions? Answering such questions is an area of intense investigation.

- For pattern formation to occur, cells and tissues communicate with each other through many different signaling pathways.
- These pathways are used repeatedly and are integrated to control specific cell fates (i.e., the eventual location and function of the cell).

Gastrulation

happens at the beginning of embryogenesis during the blastula stage after 2 weeks of gestation till the end of fourth week

- Gastrulation is the process of cell and tissue movements whereby the cells of the blastula are rearranged so that they have new positions and neighbors.

- In the human embryo, gastrulation occurs between days 14 and 28 of gestation.

- In this process, the embryo is transformed from a zygote then a few cells into a three-layer (trilaminar) structure composed of three germ layers: ectoderm (outer layer), endoderm (inner layer), and mesoderm (middle layer). During gastrulation, the two-layered structure of the blastula is transformed into a three-layered structure called the gastrula.
- The formation of these layers is a prerequisite for the next phase of development, organogenesis.

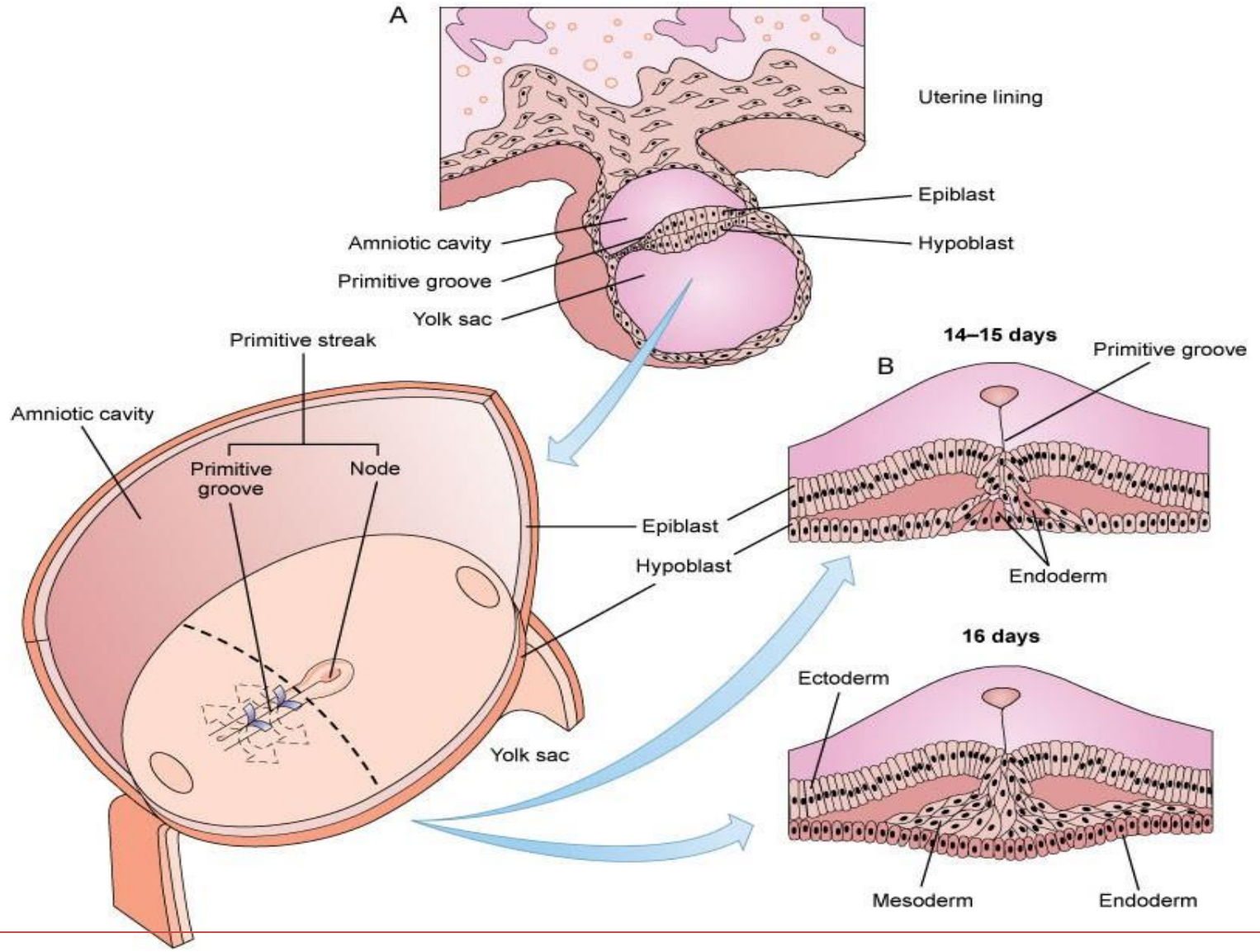


Fig. 10-4. Human gastrulation. **A,** Sagittal section through the midline of an embryo embedded in the uterine lining. **B,** Dorsal surface of an embryo exposed by removing part of the embryonic mesoderm surrounding the amniotic cavity and yolk sac. *Arrows* denote ingressing epiblast cells. On days 14 to 15, epiblast cells replace hypoblast cells to form endoderm. A day later, migrating epiblast cells are creating a layer of mesoderm.

This yolk sac contains primitive groove of blastula

14-15 days after fertalization blastula differentiates into epiblast and hypoblast . By day 16 epiblast migrates inward to form three layers (ectoderm, mesoderm, endoderm) at day 16. The formation of these layers marks the beginning of gastrulation
(Migrating epiblast creates layer of mesoderm)

- The major structural feature of mammalian gastrulation is the **primitive** streak, which appears as a thickening of epiblast tissue extending along the anterior-to-posterior axis.

- In placental animals such as humans, gastrulation includes formation of the extraembryonic tissues. Extraembryonic tissues are structures that support the developing embryo but are not part of the embryo itself. These tissues originate from the zygote and play crucial roles in nutrition, gas exchange, waste removal, and protection (ChatGPT)

- The process of gastrulation is dominated by cell migration. So, many of the genes expressed during gastrulation encode proteins that facilitate cell movement.

Neurulation and Ectoderm

- Once a trilaminar embryo is formed, the dorsal mesoderm and the overlying ectoderm interact to form the hollow neural tube. This event, called neurulation, is mediated by induction. Any defect in neuulation leads to neurological problems could be seen by ultra sound during pregnancy

- Induction is the process by which cells of one embryonic region influence the organization and differentiation of cells in a second embryonic region.

- In amphibians, induction of the neural tube and transformation of the flanking mesoderm to create an embryo with clear **anterior/ posterior and dorsal/ventral axes** is controlled by a group of cells known as the Spemann–Mangold organizer. This field remains unclear and is still being actively researched

- A number of proteins are expressed almost exclusively in the organizer. Chordin is a secreted protein that prevents dorsalized mesoderm from being ventralized. Another secreted protein, Noggin, induces neural tissue from dorsal ectoderm and dorsalizes the mesoderm.

- Neurulation is a critical event in development because it initiates organogenesis and divides the ectoderm into three different cell populations:

(1) the neural tube, which will eventually form the brain and spinal cord,

(2) the epidermis of the skin, and

(3) the neural crest cells.

- Defects of neural tube closure and neural crest migration or differentiation cause birth defects.

Mesoderm and Endoderm

- Formation of a layer of mesoderm between endoderm and ectoderm is one of the major events of gastrulation.

- Mesoderm can be divided into five components: the notochord; the dorsal, intermediate, and lateral mesoderms; and head mesenchyme.

Components of mesoderm

The notochord	Is a transient midline structure	That induces the formation of the **neural tube** and **body axis**☺ دكتور محمد السالم .
dorsal mesoderm	The adjacent dorsal mesoderm on either side of the notochord	Differentiates into elements that form the **axial skeleton** ,**skeletal muscles** evticennoc dna , eht fo eusst**iskin** SSM .
Intermediate mesoderm		Forms the **kidneys** and **genitourinary** system. UGS
Lateral plate mesoderm		differentiates into the **heart**, the the **appendicular skeleton**, the connective tissue of **viscera** and the **body wal**l, and the connective tissue elements of the **amnion** and **chorion**nimodbA.
head mesenchyme.		Finally, the muscles of the **eyes** and **head** arise☺ دكتورة هبة

Mesoderm and **Endoderm**

- The primary function of embryonic endoderm is to form the **linings** of the **digestive tract** and the **respiratory tree.** **RS and GI**

- Outgrowths of the intestinal tract form the pancreas, gall-bladder, and liver. A bifurcation of the respiratory tree produces the left and right lungs.
- The endoderm also produces the **pharyngeal pouches**, which, in conjunction with cells derived from the neural crest, give rise to **endodermal-lined** structures such as the middle ear, thymus, parathyroids, and thyroid.

2.Axis specification

- Animal body plans have evolved into a wide variety of sym metries.
- Some animals, such as the sea anemones, are completely symmetrical.
- Other animals (e.g., starfish) exhibit only a dorsal/ventral symmetry.
- Many animals, such as worms, add an anterior/posterior axis.
- All chordates (animals that develop a notochord) have a third axis that is perpendicular to the first two, the left/right axis.

More complex animal shows more axes

- Specification and formation of these axes are critical events in development because they determine the orientation of the body plan. The proteins mediating these processes are rapidly being discovered.

(Many fibroblast growth factors involve in mesodermal and endodermal derived structures and functions)

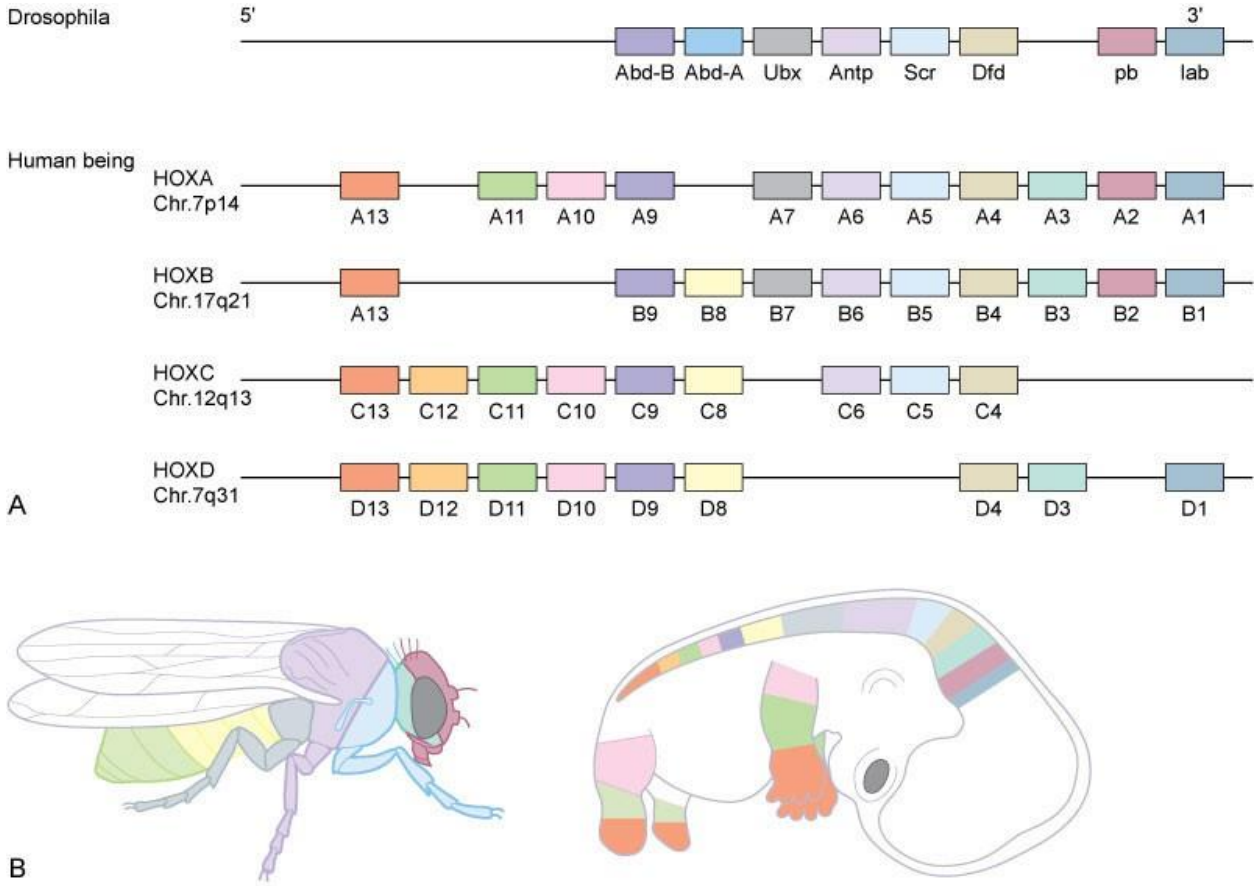
Formation of the Anterior/Posterior Axis

- The anterior/posterior axis of a developing mammalian embryo is defined by the primitive streak and patterned by combinations of **Hox** genes.

- Collectively these combinations identify various regions along the anterior/posterior axis of the body and limbs.

- Disruption of **Hox** genes produces defects in body**, limb, and organ patterning.**

-There is 4 groups of HOX genes that encodes transcription factors and control anterior posterior axes and so on.



(Modified from Verakas A, Del Campo M, McGinnis W: Developmental patterning genes and their conserved functions: From model organisms to humans. Mol Genet Metab 2000;69:85-100, with permission.)

Fig. 10-5. **A,** Distribution of 8 Hox genes in a single cluster in *Drosophila* and 39 Hox genes among clusters on 4 chromosomes in human (*HOX*). Individual Hox genes are labeled from 1 (3') to 13 (5') within each cluster. Hox genes that share the same number but are located in different clusters are called *paralogs* (e.g., *HOXA13* and *HOXD13* are paralogs). Paralogs often exhibit more sequence homology than do different Hox genes in the same cluster. Hox genes are expressed from 3' to 5' along the anterior/posterior axis of the embryo, and Hox genes located 3' are expressed earlier than Hox genes located 5'. **B,** Schematic diagram of combinatorial codes of overlapping Hox gene expression domains along the anterior/posterior body axis. Hox codes determine the identity of each segment. Thus, if expression of *Hoxb4* is eliminated (e.g., in a knockout), the combinatorial code in the third segment is altered from 1 + 2 + 3 to 1 + 2. This results in transformation of the third segment into another second segment. The transformation of one structure into another is called a homeotic transformation.

Figure compares HOX genes of embryo and dorsophila, 8 HOX genes is present in dorsophila, 39 HOX genes in Human.

-Colors indicates activated genes at specific positions.

-8 HOX genes is common between dorsophila & human, while human has extra complicated genes.

Formation of Ventral/Dorsal Axis

- Dorsal/ventral patterning of the embryo is an active process that is coordinated by signaling molecules and their antagonists.

- Dorsal/ventral patterning of the vertebrate depends on the interaction between dorsalizing and ventralizing signals.

- ***noggin* and *chordin*** encode secreted proteins that are capable of **dorsalizing** ventral mesoderm and restoring dorsal structures that have been ventralized.
- ***Bmp*-4** is expressed ventrally and induces **ventral fates**, patterning the dorsal/ventral axis.
- Noggin and chordin bind directly to Bmp-4 to prevent it from activating its receptor. So, the organizer promotes dorsalization by repressing a ventralizing signal encoded by *Bmp*-4. (There is need for many genes interactions to enable correct axes differentiation)

Craniofacial Development

- The majority of craniofacial structures are derived from neural crest cells.
- Neural crest cells from the forebrain and midbrain contribute to the nasal processes, palate, and mesenchyme of the first pharyngeal pouch. This mesenchyme forms the maxilla, mandible, incus, and malleus.

- The fate of each group of neural crest cells is specified by **homeobox-**containing genes.
- Some of the genes controlling craniofacial development have been isolated by analysis of **craniosynostosis syndromes**.

Development of the limb

- The vertebrate limb is composed of elements derived from lateral plate mesoderm and somitic mesoderm.

- Growth and patterning are controlled by proteins secreted from specialized collections of cells called the apical ectodermal ridge, the progress zone, and the zone of polarizing activity.

.3Organ Formation

- Formation of organs involves reciprocal interactions between epithelium and mesenchyme.

- This interaction is mediated by secreted signaling molecules that bind to receptors, conduct signals through various interconnected pathways, and stimulate or repress **DNA** transcription. Switching on & off happens to facilitate organ formation

- Once a specialized cell within an organ is terminally differentiated, various proteins turn on its molecular machinery so that it may perform its intended function. Often, development of the organ and function of the differentiated cell are interrelated.

- Interactions between **mesenchymal and epithelial cells** are prominent in the development of **cutaneous structures** (e.g., hair, sweat glands, breasts), **parenchymal organs** (e.g., liver, pancreas), lungs, thyroid, kidneys, and teeth.

- The integrity of signals exchanged between the epithelium and the mesenchyme is dependent on the integrity of these tissues. Several proteins produced within the epithelium are known to promote the growth and differentiation of the epithelium.

- One of the largest organs in the body is the skeleton. **Skeletal** formation is dependent on bone-forming cells called osteoblasts.
- The differentiation of osteoblasts is regulated by an **osteoblast-**specific transcription factor, **Runx2**. Targeted disruption of Runx2 produces mice with a complete lack of ossification of the skeleton.

If we used mouse as a model animal and blocked Runx2, it results in lack of ossification

This lecture have mentioned classification of many genes that involves in developmental process of axes, organs & tissues and their interactions. Each main class of **developmental genes** was **discovered** through **animal studies** & compared to human ones which are more complex and any genetic defect will impede developmental proceses and produce congenital malformations. After completion of embryogenesis all developmental genes are switched off.

Additional sources

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2			
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!