MUSCULOSKELETAL DEVELOPMENT

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OVERVIEW

Intraembryonic mesoderm – sandwiched between ectoderm and endoderm in trilaminar disk

Extraembryonic mesoderm - Mesoderm lying outside the embryo proper and involved in the formation of amnion , chorion , yolk sac, and body stalk.

Extraembryonic mesoderm form two layers

1. Somatic layer/ Parietal layer/ Outer layer develops adjacent to cytotrophoblast
2. Splanchnic layer/ Visceral layer/ Inner layer develops adjacent to hypoblast

Laterally, intraembryonic mesoderm is in contact with extraembryonic mesoderm.

From 3rd week onwards, the medial most part of intraembryonic mesoderm (adjacent to neural tube and notochord) proliferates and become swollen and larger in size, which is then called **paraxial mesoderm**.

Next to the paraxial mesoderm, **intermediate mesoderm** is present.

The outer part is called **lateral plate**. The lateral plate develops cavities and is divided into two layers. The plate related with ectoderm is called somatic layer while the layer related with endoderm is called splanchnic or visceral layer. The cavity, which is developed between the two layers is called **intraembryonic coelom**. With time, this intraembryonic coelom eventually becomes continuous with extraembryonic coelom.

In further development, folding of trilaminar disk takes place.

The endodermal lining will develop into GIT.

The splanchnic layer of lateral plate will develop into musculature of wall of GIT.

The endodermal lining will develop into skin.

The somatic layer will convert into musculature of body wall and here ribs will develop.

The intraembryonic coelom will eventually differentiate in abdomen into peritoneum cavity and in thorax, it will develop into pleural cavity and pericardial cavity.

DEVELOPMENT OF BONES

The paraxial mesoderm undergo segmentation and each segment is called **somite**. The uppermost segments (present right under occipital area) are called **occipital somatomeres**.

The epithelial cells of ventromedial surface of somites become loose, convert into **mesenchyme** by losing their epithelial nature and starts migrating towards the notochord and neural tube. This part of somite is called **sclerotome**.

The dorsolateral portion of somite are called **dermomyotome**. The outer layer of dorsolateral portion move under the endoderm and make dermis of the skin and hence this area is called **dermatome**. The inner layer of dorsolateral portion develop into muscles, hence called **myotome**.

The cells of sclerotome which are moving medially towards neural tube will eventually help in formation of vertebral column.

The mesenchyme which is derived from sclerotome of occipital somites, will contribute to the formation of skull.

Neural crest cells are present lateral to the neural tube. These neural crest cells migrate upward and contribute to the formation of mesenchyme which will become part of skull.

Bones are developed from mesenchyme (embryonic connective tissue). Most of the mesenchyme is derived from paraxial mesoderm and visceral and somatic layers of intraembryonic mesoderm. Some mesenchyme is derived from neural crest cells.

Skull develops from mesenchyme derived from neural crest cells, as well as mesenchyme derived from occipital somatomeres.

Ectoderm moves externally along with dermatome and develop limb buds. The mesoderm of the limb is derived from lateral plate. Hence the mesenchyme of the limb develops from somatic layer of lateral plate of extraembryonic mesoderm.

DEVELOPMENT OF SKULL

Neurocranium – housing the brain

Viscerocranium – facial bones

DEVELOPMENT OF NEUROCRANIUM

Neurocranium has a vault and a base.

Mesenchyme derived from neural crest cells and mesenchyme derived from paraxial mesoderm (derived from occipital somatomeres) make fibrous membrane around CNS. This fibrous membrane eventually converts into bone. Mesenchyme coverts into bone by direct pathway and an indirect pathway.

In direct pathway i.e. **intramembranous ossification**, fibroblasts directly converts into osteoblasts

In indirect pathway i.e. **endochondral ossification**, fibroblast first convert into chondroblast and these chondroblasts later convert into osteoblasts.

Development of vault of skull is by intramembranous ossification. Due to this reason, vault of skull is called **membranous neurocranium**.

Development of base of skull is by endochorndral (intracartilagenous) ossification. Due to this reason, base of the skull is called **chondocranium**.

Sella turcica is a depression in the sphenoid bone, containing the pituitary gland.
In **prechordal chondrocranium (**area from sella turcica and anteriorly towards vault of skull), all the mesenchyme is derived from neural crest cells.
In **chordal chondrocranium** (area from sella turcica and posteriorly towards vault of skull), all the mesenchyme is derived from paraxial mesoderm (derived from sclerotome of occipital somatomeres)

In newborn babies, the bones are held together by special type of dense connective tissues called **sutures**. When two or more sutures join together, large membranous structure called **fontanelles** are produced.

Names of sutures:

1. Sagittal suture – connects two parietal bones
2. Lambdoid suture – connects parietal bones with occipital bone
3. Coronal suture – connecting frontal bone with parietal bones

Importance of sutures:

1. During the delivery, they allow the skull bones to overlap with each other and reduce the size of the skull so that baby can pass through the birth canal easily.
2. The anterior fontanelle can be used to assess the intracranial pressure. If intracranial pressure is very high in baby, it will bulge out. If intracranial pressure is low, it will bulge in.
3. The palpation of anterior fontanelle can provide estimation of bone development in infant, as normally it should close around the age of 2 years.
4. Sutures in development and enlargement of skull.

DEVELOPMENT OF VISCEROCRANIUM

Development of all facial bones is intramembranous.

Development of viscerocranium is basically from **branchial/ pharyngeal arches**. Branchial arches are specialized structures which are made during the development of head and neck. These branchial arches have a lot of mesoderm. These branchial arches also have migrated neural crest cells.

First pharyngeal arch has two components: dorsal (located superiorly) and ventral (located inferiorly)

Dorsal component will lead to the development of maxilla, zygomatic and some part of temporal bone. The mesenchyme, which will contribute to the formation of these bones, is derived from migrated neural crest cells. Two bones of inner ear i.e. malleus and incus are derived from first pharyngeal arch.

In the **ventral component** of first pharyngeal arch, a special type of cartilage called **Meckel's cartilage** is developed. Around this Meckel's cartilage, there is mesenchyme which undergoes intramembranous ossification to make mandible. The Meckel's cartilage later disappears.

Second pharyngeal arch make some structures in the neck. The dorsal part of second pharyngeal arch makes the third bone of inner ear called stapes.

Newborn baby Viscerocranium Features:

1. Lack paranasal sinuses
2. Underdeveloped jaw (absence of teeth)
3. Small mandible

CLINICAL CORRELATES OF SKULL

1. CRANIOSCHISIS

Cranioschisis – open cranium

Three types of cranioschisis:

a) Anencephaly

It is neural tube defect that occurs when rostral (head) end of neural tube fails to close, usually between 23rd and 26th day following conception. Anencephaly is the absence of major portion of brain, skull and scalp that occurs during embryonic development.
The baby with anencephaly dies before birth or shortly after birth.

b) Meningocele

Sometimes, only a part of skull vault is missing while CNS and dura mater present inside is normal. Due to the missing portion of skull, a gap is created from where dura mater comes out and CSF is present in this protrusion. This condition is called meningocele.

c) Meningomyelocele

If within the meningocele, brain substance also herniate, it is called meningomyocele.

2. SYNOSTOSIS

The condition in which sutures close prematurely.

a) Scaphocephaly/ Dolecephaly

- Premature closure of sagittal suture
- Elongated skull (due to only anterior and posterior development)

b) Oxycephaly / Acrocephaly

- Coronal suture closes prematurely
- Skull develops backward and upward
- Tower skull

c) **Brachycephaly**
   - Coronal and lambdoid sutures closes prematurely
   - Short skull

d) **Plegiocephaly**
   - Unilaterally coronal and lambdoid sutures are closed prematurely
   - Skull develops asymmetrically

3. MICROCEPHALY

- Under development of brain
- Child is mentally retarded

DEVELOPMENT OF LIMBS

Limb buds start to develop by the end of 4th week. Limbs develop in three ways:

1. Proximodistal development
2. Anterolateral development
3. Dorsoventral development

PROXIMO-DISTAL DEVELOPMENT OF LIMBS

Positioning of limb buds is determined by the expression of **Hox genes**. Ectoderm protrudes out from the area where Hox genes are expressed and somatic layer of lateral plate of intraembryonic mesoderm moves inside this protrusion.

TBX genes and fibroblast growth factors from the lateral plate initiates the growth of limb buds.

Further elongation and growth of limbs is done by **BMPs (Bone Morphogenic Protein)** produced by ectodermal lining of limb buds. Due to BMPs, ectoderm at limb apex become thick and make a thickened ectoderm ridge called **Apical Ectoderm Ridge (AER).** This ridge is limb elongator. The AER produce fibroblast growth factors which act on underlying mesodermal cells and force those cells to multiply very rapidly and doesnot allow these cells to differentiate. These mesenchymal cells right under the AER is called **progress zone**. The mesenchyme other than progress zone (located proximally to the shoulder region) start differentiating as AER effect is not significant here. Cartilaginous models start appearing in the proximal mesenchyme of limb, as ossification in limb is endochondral ossification.

When the limb has acquired its expected length, some cells in AER undergo apoptosis in four areas and AER is divided into small spots. These spots start inducing the underlying mesenchyme and the progress zone moves into these five areas (five digits). Eventually AER degenerates and further growth of digits stop.

ANTERO-POSTERIOR DEVELOPMENT OF HAND

Fetus thumb is located anteriorly while little finger is located posteriorly.

In medial part of limb there is special group of cells called **zone of polarizing activity (ZPA).** It secretes Vitamin A and express special genes which produce **sonic hedgehog**. This sonic hedgehog is responsible for development of special sequence of digits (from little finger to thumb). The high concentration of sonic hedgehog produce little finger on medial aspect of hand (due to location of sonic hedgehog medially) while the low concentration of sonic hedgehog in thumb area produce thumb.

DORSO-LATERAL DEVELOPMENT

The dorsal and lateral development of hand is due to production of certain growth factors

BONE DEVELOPMENT OF LIMB

The **primary ossification centres** develop in shaft (diaphysis) of cartilaginous models after 7th embryonic week. Just after birth, **secondary ossification centres** develop in epiphysis area in cartilaginous models and develop epiphysis of bones.

Epiphyseal plate (area between epiphysis and diaphysis) is not ossified for many years. The chondrocytes in epiphyseal plate keeps proliferating for many years and provide mechanism for elongation of bones.

CLINICAL CORRELATES WITH LIMB DEVELOPMENT

1. **Amelia** – no limbs
2. **Meromelia** – limb is abnormal in proportion
3. **Micromelia** – normal proportion but miniature limbs
4. **Phocomelia** – hands and feet attached directly through some irregular bones i.e. arm and forearm is absent
5. **Achondroplasia** – the epiphyseal plate of long bones close prematurely so limbs do not grow even though normal development of trunk and skull takes place (dwarfism). It is more common when paternal age is too much.
6. **Club Foot** – can be inherited or developed due to abnormal position of fetus in uterus. Newborn's foot or feet appear to be rotated internally at the ankle.
7. **Congenital Dislocation of Hip Joints** – in these female babies, acetabulum is very shallow and small, head of the femur is also small and capsule of the hip joint is very loose. It is commonly seen in those female babies which are delivered in breech position (babies lying bottom first or feet first in the uterus instead of the usual head-first position)
8. **Polydectaly** – more than five fingers
9. **Ectrodectaly** – less than five fingers
10. **Brachydectaly** – short fingers due to early degeneration of AER spots
11. **Syndectaly** – fused digits because AER doesnot degenerate between fingers
12. **Claw Hands** – AER of middle finger does not develop due to which middle finger along with its metacarpal is absent. The thumb and index finger are fused while little finger and ring finger are fused. As a result the appearance of hand is claw-like.

DEVELOPMENT OF VERTEBRAL COLUMN

The somites of paraxial mesoderm are present bilaterally to neural tube and notochord. Sclerotome, dermatome and myotome arise from somites. Mesenchyme derived from sclerotomes move medially and eventually surround the notochord and neural tube. The mesenchyme which surrounds the neural tube makes **vertebral arches**. The mesenchyme surrounding notochord will make **vertebral body**.

Segmental arrangement of sclerotomes change drastically at this point. Every sclerotome derived from each somite (segment) divide into upper and lower part. Lower half of each sclerotome fuses with the upper half of adjacent lower sclerotome. The mesoderm between upper and lower half does not proliferate, hence the development of vertebrae is intersegmental. The neural spinal nerves moves through mesodermal area between sclerotomes. The myotome surrounds the vertebral body and thus help in movement of spine.

Notochord degenerates in areas where vertebral column is developing. But in between vertebrae i.e. in intervertebral area, notochord will expand called **nucleus pulposis** and fibrous tissue will form around it called **annulus fibrosis**.

REMEMBER:

The sclerotome forms the vertebrae, rib cartilage and part of occipital bone.

The myotome forms the musculature of back, ribs and limbs.

The syndetome forms the tendons.

The dermatome forms the skin on back

CLINICAL CORRELATES WITH VERTEBRAL COLUMN

1. SCOLIOSIS

S-shaped or side ways curvature of the spine. May be due to degeneration of one of the vertebral segment or abnormal fusion of vertebral segments with each other.

2. SPINA BIFIDA

Spina bifida is a birth defect that occurs when the spine and spinal cord don't form properly. It's a type of neural tube defect. The neural tube is the structure in a developing embryo that eventually becomes the baby's brain, spinal cord and the tissues that enclose them.

Normally, the neural tube forms early in pregnancy and it closes by the 28th day after conception. In babies with spina bifida, a portion of the neural tube doesn't close or develop properly, causing defects in the spinal cord and in the bones of the spine.

TYPES OF SPINA BIFIDA:

a) **SPINA BIFIDA OCCULTA -** "Occulta" means hidden. It's the mildest and most common type. Spina bifida occulta results in a small separation or gap in one or more of the bones of the spine (vertebrae). Many people who have spina bifida occulta don't even know it, unless the condition is discovered during an imaging test done for unrelated reasons

b) **SPINA BIFIDA CYSTICA -** A bony defect in the vertebral column that causes a cleft in that column. The meningeal membranes that cover the spinal cord and part of the spinal cord protrude through this cleft, and are clearly visible.

   Myelomeningocele is the most severe type. The spinal canal is open along several vertebrae in the lower or middle back. The membranes and spinal nerves push through this opening at birth, forming a sac on the baby's back, typically exposing tissues and nerves. This makes the baby prone to life-threatening infections and may also cause paralysis and bladder and bowel dysfunction.