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Embryonic development: week 3

Introduction

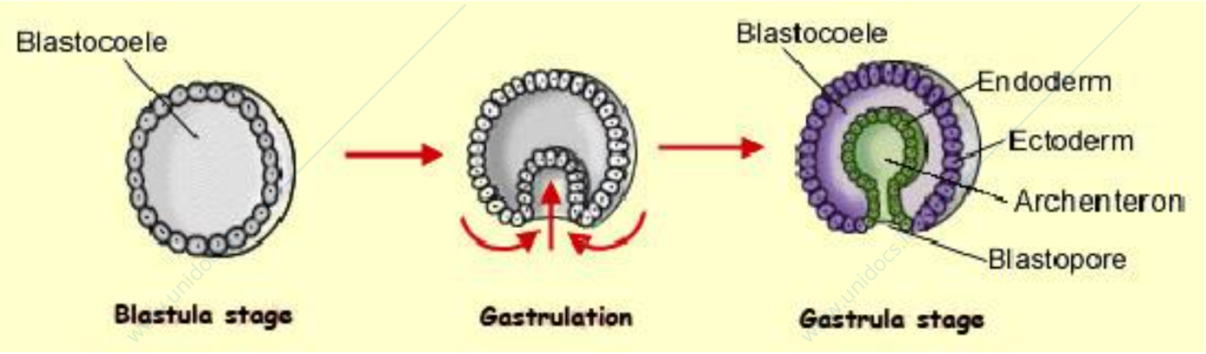
The third week of embryonic development is characterized by several significant events which will set the stage for the subsequent development of organ systems and tissues.

These events include: gastrulation, formation of the notochord, neurulation, mesoderm formation, coelom formation
and embryonic folding. Many of these processes begin in the third week and continue into the fourth week. By the end of the 4th week, the embryo is ready to begin organogenesis. Therefore, in the weeks to follow, specific organ systems will be developed. The embryonic period continues until the eighth week of development. During the embryonic period, but in particular the 3rd and 4th weeks, the embryo is at its greatest risk for developmental defects, in particular due to environmental factors. From the eighth week until birth is the fetal period, a time characterized by growth of the organ systems started in the embryonic period.

GASTRULATION

Like many other phases of embryological development, gastrulation is a complex, biochemically dependent process by which the bilaminar embryo acquires a third layer to become a trilaminar disc.
It is not uncommon to hear some individuals refer to the embryo as a gastrula during this developmental phase. During this process, the embryo also develops axial inclination. This process also contributes significantly to the morphological changes that the embryo will go through in order to acquire a human shape.
Gastrulation begins when a linear region of cells of the epiblast layer become thicker at the caudal aspect of the embryo. This primitive (Spemann's) streak develops as epiblast cells replicate and migrate to the midline of the bilaminar disc under the influence of nodal. Nodal is a transformation growth factor β (TGF β) protein that not only initiates, but also maintains the primitive streak. The streak is comprised of totipotent stem cells from the epiblast that grow in a caudocranial manner.

As cells are added to the caudal end of the primitive streak, the cranial end begins to enlarge and forms a primitive (Hensen's) node. Simultaneously, a thick depression develops within the streak that is continuous with the sunken area at the primitive node (i.e. the primitive groove and primitive pit, respectively). The establishment of these structures allow identification of the cranial (near the primitive node) and caudal (towards the tail of the primitive streak) poles of the embryo. It also facilitates the identification of the left and right sides, as well as dorsal and ventral surfaces of the embryo.



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GERM LAYERS

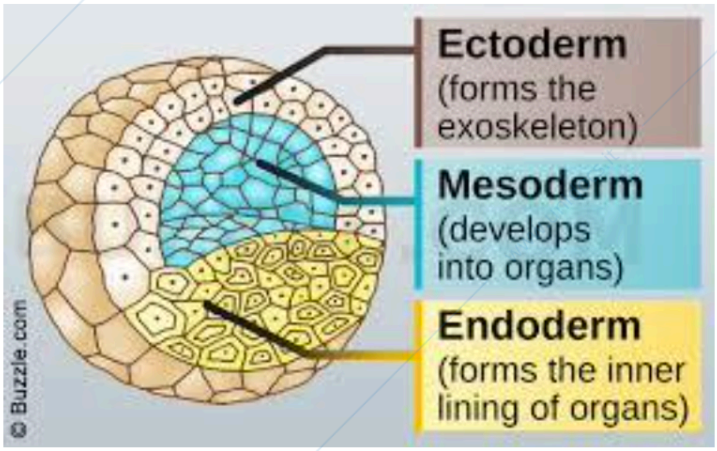
The cells of the primitive streak synthesize and secrete fibroblast growth factor 8 (FGF8). FGF8 downregulates the expression of E-cadherin, which is intended to promote cellular adhesion. As a result, epiblast cells that have lost their adhesion molecules will subsequently undergo invagination.

Not only does this give rise to the previously described depressions (primitive groove and pit), but it also results in migration of epiblast cells between the epiblast and the hypoblast layers. These cells lose their tall columnar appearance and become loosely arranged spindle-shaped cells suspended in collagenous reticular fibers known as mesenchyme. The mesenchyme is made up of pluripotent cells that will provide structural support for the embryo.

They also have the ability to differentiate into osteoblasts, chondroblasts, and fibroblasts, in addition to participating in vasculogenesis and angiogenesis. FGF8 stimulates the expression of another protein, called Bachyury T, which regulates the transformation of other mesenchyme cells to the middle embryonic layer known as the mesoderm.

As other epiblast and primitive streak cells migrate deeper, they eventually displace cells of the hypoblast to form the embryonic endoderm. The cells remaining in the epiblast are subsequently referred to as the ectoderm. Therefore, all three germ layers of the gastrula are epiblast derivatives.

The mesoderm will eventually separate the ectoderm from the endoderm, except at the points where the two layers are. The cloacal membrane is a circular structure that marks the future location of the anus. On the other hand, the prechordal plate gives rise to the oropharyngeal membrane (also a bilaminar region), which will form the future mouth and pharynx.



FUNCTION OF THREE GERM LAYERS

The three germ layers are responsible for forming all tissues within the body, in particular:

Embryonic ectoderm, located on the external region of the embryo, gives rise to central and peripheral nervous system (neurulation); sensory epithelia of the eyes, ears and nose; the epidermis and it's appendages (hairs, nails); mammary and subcutaneous glands; hypophysis and the enamel of the teeth.

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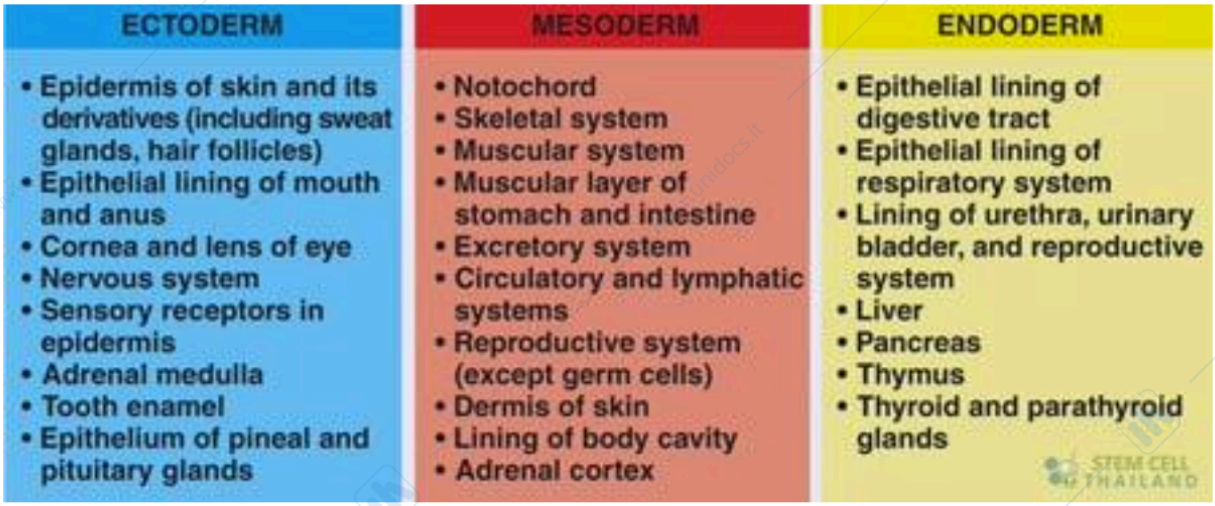
Embryonic mesoderm gives rise to paraxial, intermediate, and lateral plate mesoderm. The lateral plate mesoderm has cardiac, haematological, vascular, and smooth muscle fates. It also gives rise to the spleen, lymphatics, and adipose tissue. Intermediate mesoderm is responsible for the formation of the lower urinary tract, kidneys, and the reproductive system. The paraxial mesoderm first form somites. The somites then differentiate into the rigid structural components of the body (i.e. bone, ligaments and tendons, cartilage and skeletal muscle). They also give rise to the dermis.

Embryonic endoderm gives rise to the aero-digestive epithelium, as well as the glandular cells of the gastrointestinal tract and its associated organs. The lungs, thymus, thyroid, and prostate glands are also derived from it.



NOTOCHORD FORMATION

As the primitive node and streak are formed, invaginating mesodermal cells migrate cranially through the structure. They become prenotochordal cells that travel cranially towards the prechordal plate, in the midline. The primitive pit then projects into the notochordal process, giving rise to the notochordal canal. The notochordal process is now a tubular structure occupying the space between the primitive node to the prechordal plate. The prenotochordal cells of the notochordal process interdigitate with the cells of the hypoblast layer, prior to the invasion of the endoderm.

The fused layer subsequently becomes perforated, allowing communication between the notochordal canal and the umbilical vesicle. As these perforations coalesce, the floor of the notochordal canal is lost.

This is followed by flattening of the remaining notochordal process to form the notochordal plate. Proliferation of the notochordal cells at the cranial end of the notochordal plate results in infolding of the tubular structure. Subsequently, a solid cord of cells that is definitively the notochord arises.

At the area where the primitive pit descends into the epiblast, the notochordal canal persists; giving rise to a neurenteric canal that provides temporary communication between the amniotic cavity above and the umbilical vesicle below. This communication is obliterated as the notochord detaches from the endoderm. The notochord projects from the primitive node to the oropharyngeal membrane.

As the primitive streak extends caudally, the notochord also follows. Therefore, acraniocaudal growth pattern of the notochord is observed. Also, note that at this stage of development, prechordal mesoderm arises from neural crest cells, just rostral to the notochord.

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Therefore, the cloacal and oropharyngeal membranes are the only bilaminar regions of the embryo that remain. Notochordal migration is also associated with movement of pluripotent mesoderm that also move cranially, bilaterally with respect to the notochord process and prechordal plate.

Once they have established a cranial position in the cardiogenic area of the embryo, the heart primordium is formed from the cardiogenic mesoderm by the end of week 3.

Functions of the notochord

- It defines the primitive longitudinal axis of the embryo.
- It contributes to the formation of the intervertebral discs. Fragments of the notochord persist into adulthood as the nucleus pulposus of the intervertebral disc.
- It plays an important role in the formation of the axial musculoskeletal system.
- It is important in the development of the central nervous system.

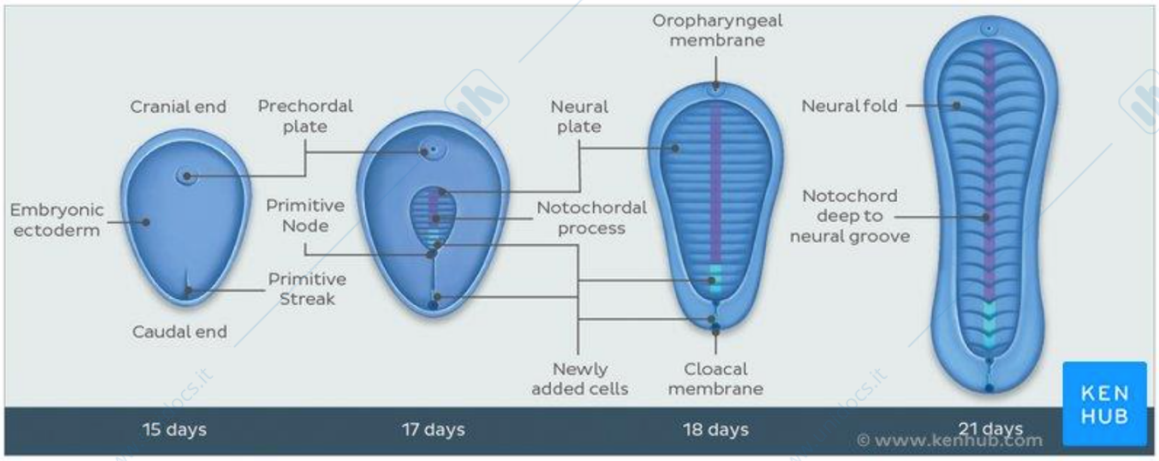
NEURAL TUBE DEVELOPMENT

Not only does the notochord influence the epiblast to migrate and form the two deeper layers, but it also stimulates regions of the ectoderm to form the neural plate.
This thick, elongated area of epithelial cells is a midline structure is adjacent to the midline and is superficially related – and equal in length – to the notochord.

Growth of the notochord corresponds with an increase in width of the neural plate. The plate also grows cranially and meets the oropharyngeal membrane until it eventually outgrows the notochord.

There is a prominent invagination along the long axis of the neural plate called the neural groove. There are raised neural folds on either side of the groove that appear more pronounced at the cranial pole; indicating early brain development has commenced. Inward migration and subsequent fusion of the neural folds occur as the third week comes to a close.

The neural plate has now become a neural tube, which serves as the primitive spinal cord and brain vesicles. Some neural crest cells that were not incorporated in the neural tube transform from epithelium to mesenchyme, after which they move away from the fusing neural folds. The underlying neural tube separates from the ectoderm and the non-neural edges of the ectoderm fuse to close the dorsum of the embryo; forming the epidermis.



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During the closure of the neural tube, there is dissociation of some underlying neuroectodermal cells at the inner border of the folds. The neural crest cells completely separate from both the surface ectoderm and neural tube during this migration process.
They aggregate as flat, irregular cells known as the neural crest that lies between the neural tube and surface ectoderm. The neural crest divides into left and right halves and migrates laterally, to the dorsal region of the embryo (relative to the neural tube).

ALLANTOIS

By the 16th day of gestation, an outpouching extending from the wall of the umbilical vesicle that is adjacent to the connecting stalk develops. This diverticulum is referred to as the allantois. In humans, it is a rudimentary structure that may be linked to pathological processes of the urinary bladder. The allantois mesoderm spreads out deep to the chorion and expresses vasculogenic potential; giving rise to the umbilical artery that will supply the placenta (the umbilical vein arises from another source). Proximally, the allantois persists throughout development as the urachus. This structure connects the urinary bladder to the anterior abdominal. In adults, the urachus is known as the median umbilical ligament.

SOMITE FORMATION

Primitive node tissues are also responsible for the formation of paraxial mesoderm. These are longitudinal blocks of cells that are medially related to the intermediate mesoderm. For completion, the lateral mesoderm is lateral to the intermediate mesoderm, but medial to the extraembryonic mesoderm of the umbilical vesicle and amnion. Under the influence of forkhead transcription factors (FoxC1 and FoxC2), along with NOTCH and HOX genes, condensation and conformational changes of the paraxial mesoderm cells at the end of week three gives rise to paired cube-like bodies of cells called somites. This development takes place craniocaudally – thanks to the Delta-Notch signaling pathway – on either side of the neural tube. By week four, the embryo will enter the somite period, where around 38 pairs of somites can be observed. This number increases to about 44 pairs by the end of week 5. Somites are unique because they produce marked elevations on the dorsal surface of the embryo. Their prominence also aids in aging the embryo during the fourth and fifth gestational weeks.

INTRAEMBRYONIC COELOM

A coelom refers to a body cavity. Therefore the intraembryonic coelom is the primitive body cavity within the embryo. Initially, they appear as solitary coelomic spaces in the lateral and cardiogenic mesoderm layers. Subsequent fusion of the spaces forms a solitary, horseshoe-like space that partitions the lateral mesoderm into two layers:

• The splanchnic lateral mesoderm is the visceral layer that is adjacent to the endoderm layer and communicates laterally with the extraembryonic mesoderm of the umbilical vesicle. Together, the two structures will form the splanchnopleure, which is the embryonic gut.

• The somatic lateral mesoderm is the parietal layer that is just deep to the ectoderm and communicates laterally with the extraembryonic mesoderm of the amnion. The two layers combine to form the somatopleure, also known as the embryonic body wall.
The intraembryonic coelom undergoes further division from the 5th gestational week, onwards. At that time, it is divided into the pericardial cavity, peritoneal cavity, and the pleural cavities.

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PRIMITIVE CARDIOVASCULAR SYSTEM

The conversion of a bilaminar embryonic disc to a trilaminar one reduces the efficacy of diffusion as the principal mode of nutrient delivery to the developing cells.
Consequently, during the third week, the embryo initiates a more efficient mechanism for nutrient transport and waste disposal.
Blood vessels arise by two major mechanisms: vasculogenesis and angiogenesis. The former refers to the formation of new blood vessels via a de novo pathway (i.e. induction and assembly of angioblasts). The latter, however, speaks to the formation of new blood vessels by budding from previously formed vessels. The development of blood itself is referred to as hematogenesis.

Blood and blood vessel formation

Vasculogenesis commences in the extraembryonic mesoderm of the connecting stalk, umbilical vesicle and chorion. It is followed briskly by embryonic vasculogenesis.
Fibroblast growth factor 2 (FGF2) is the primary instigator for vasculogenesis.
By binding to fibroblast growth factor receptors (FGFR) on mesoderm, it induces their differentiation into hemangioblasts. These pluripotent cells then aggregate in the yolk sac and give rise to blood islands.
With the action of vascular endothelial growth factor (VEGF) acting on vascular endothelial growth factor receptors (VEGF-R2), hemangioblasts eventually differentiate into endothelial cells.
VEGF then acts on VEGF-R1 in order to stimulate the characteristic tubular arrangement of the endothelial cells in the blood vessels.

Primitive heart formation

As the blood and blood vessels begin to form, there is a concomitant establishment of the cardiogenic area. A pair of longitudinal tubes with endothelium called the endocardial heart tubes are formed during this time.
They eventually fuse to form the primordial heart tube. It merges with embryonic and extraembryonic blood vessels to establish the primordial cardiovascular system. In most cases, heartbeats commence at the end of week three, making the heart the first functional organ of the embryo. However, this heartbeat is not readily appreciated until the 5th week of gestation.

Chorionic villi

The primary chorionic villi first appear as the 2nd week ended. Following this event, they are invaded by mesenchymal tissue as they began to arborize.
The now secondary chorionic villi extend across the entire chorionic sac.
These mesenchymal cells also have vasculogenic and hematogenic potential and subsequently differentiate into capillaries and blood cells. Once the blood vessels become visible, the structures are called tertiary chorionic villi.
There is subsequent fusion of the capillaries that gives rise to the arterio-capillary network. These networks will eventually communicate with the primordial heart tube by the end of week 3.
Feto-maternal exchange of nutrients and waste material can now be facilitated at the villous interface instead of the previous diffusion gradients.
The trophoblast also continues to grow such that proliferation of the cytotrophoblast results in projection of the villi through the syncytiotrophoblast. This gives rise to an extravillous cytotrophoblastic shell that encircles the chorionic sac and further embeds into the endometrium.

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Gross morphological changes of the embryonic disc

Not only does the embryonic disc now have three layers, but it has also increased in length and (in some areas) width. The previously flat circular disc elongates and becomes broad at the cephalic pole, but slender at the caudal region. The increased width at the cephalic end is attributed to the constant cellular migration to this area.

The invagination migration sequence occurring at the primitive streak continues to progress into the 4th gestational week. It is interesting to note that while there is cessation of gastrulation cranially, the process persists in the caudal region. This phenomenon is related to the fact that cellular specialization in the cranial region precedes that same process caudally. Therefore, the primitive streak continues to undergo growth and promote gastrulation in the caudal segment of the embryo.

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