

EMBRYOLOGY

Stages of Embryology

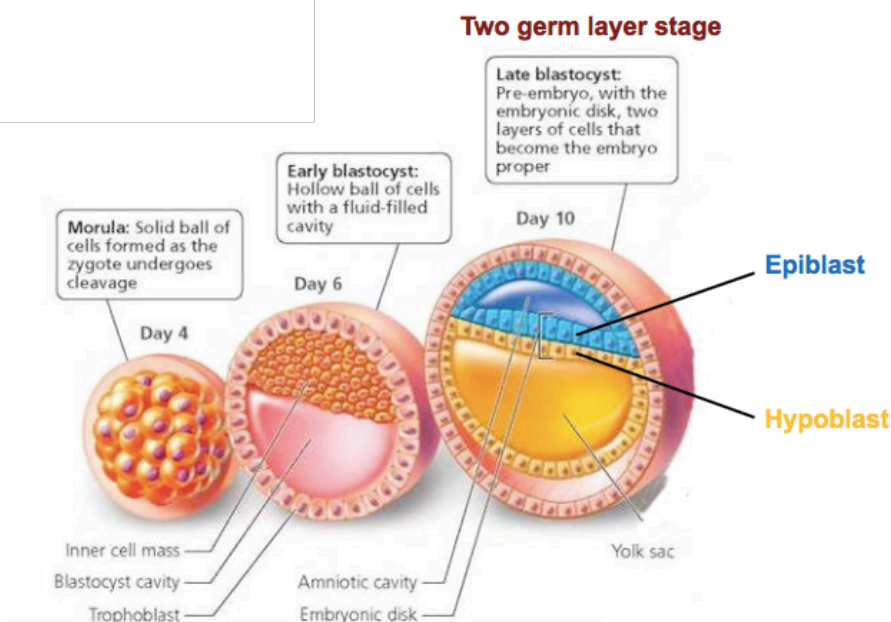
Egg	Fertilization – week 2
Embryo	Week 3 – week 8
Foetus	3 rd month – birth

Stages of Early Development

1. Ovulation = 2^o oocyte is released from the ovary and is swept into the oviduct
2. Fertilization = sperm penetrates oocyte and they fuse to form a zygote
3. Cleavage = rapid mitotic divisions as the zygote moves towards the uterus
4. Morula = solid ball of cells entering the uterus
5. Blastocyst = hollow ball of cells with a fluid filled cavity, freed from the zona pellucida and can increase in size
6. Implantation = blastocyst attaches to the endometrium and 3 germ layers form

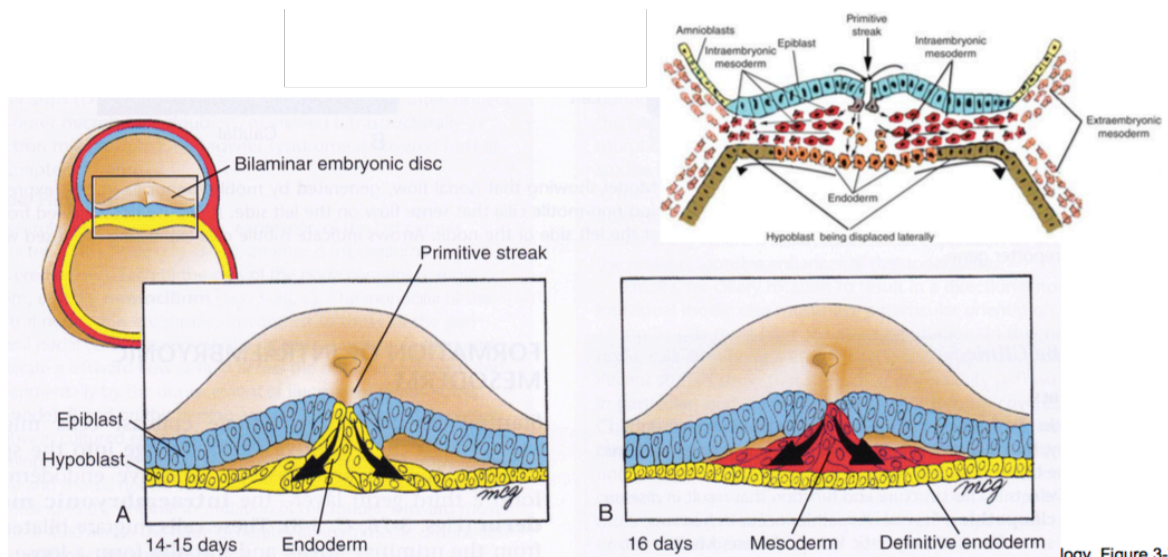
Blastocyst

- Initially contains 2 types of cells:
 - Trophoblast = outer epithelial layer, goes on to form extra-embryonic structures
 - Embryoblast/inner cell mass = goes on to form embryo
- Blastocyst then goes on to form 2 germ layers from the splitting of the inner cell mass into:
 - Epiblast
 - Hypoblast
- Between these 2 germ layers is the embryonic disc, which goes on to form the embryo



Gastrulation

- The process of the blastula becoming a gastrula as it forms 3 germ layers
- Begins with the formation of the primitive streak on the dorsal side
- Primitive streak
 - Line of thickened cells which appear on the epiblast
 - Defines all major body axes
- Primitive streak invaginates to form the primitive groove
- Cells migrate through the primitive groove to form the 3 germ layers:
 - First cells which migrate replace the hypoblast and form the endoderm
 - Next cells migrate into the space between the epiblast and endoderm to form the mesoderm
 - Remaining epiblast cells form the ectoderm
- As cells migrate through the primitive streak, they distribute evenly



logy, Figure 3-7

Primitive node

- Located at the end of the primitive streak
- Fluid filled
- Sets up left-right asymmetry
- Rotating cilia inside the node cause leftward fluid flow
- How does this leftward fluid flow break symmetry and indicate to the cells which side they're on?
 - Morphogen hypothesis = fluid pushed to the left has molecules in it which bind to receptors and signal to cells which side they're on
 - Node vesicular parcel hypothesis = molecules in the fluid are in vesicles
 - Two cilia hypothesis = cilia at the bottom of the node rotate, while cilia at the top are non-motile and sense motion to signal to the cells which side they're on
- Confusion of what side of body axes cells are on can cause sinus invertus disorders

ECTODERM

Neurulation is the process by which the neural plate and neural tube are formed

Neural Plate

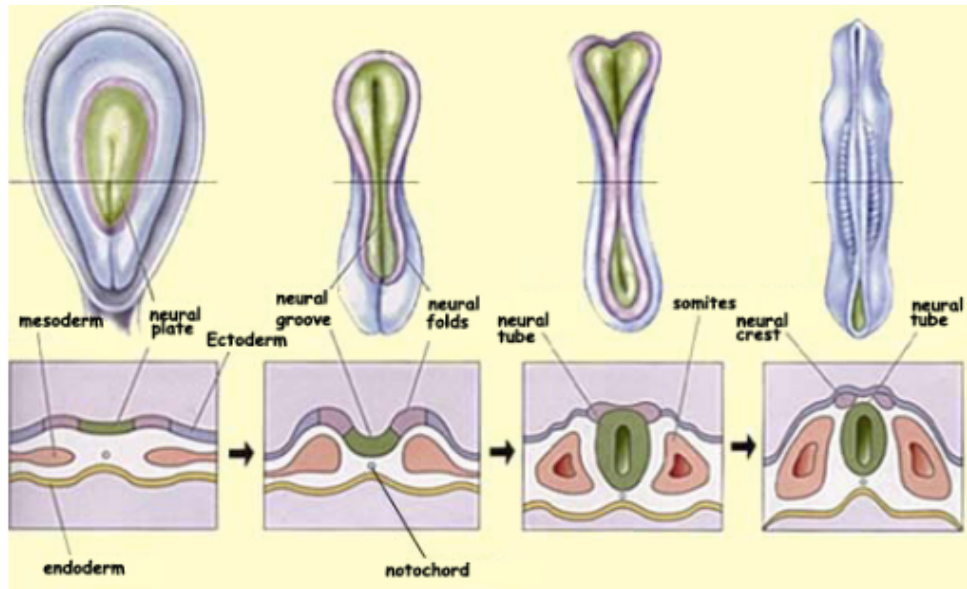
- Formation of the neural plate is induced by the notochord
- Located from the cranial end to primitive node
- Ectodermal cells above the notochord differentiate into a thick plate of pseudostratified epithelial cells
- This forms the neural plate

Neural Tube

- Extension and invagination of the neural plate causes the formation of a neural groove
- Groove closes to form neural tube

Neural Crest

- Located where neural folds meet
- Once the tube is closed, cells undergo epithelial → mesenchymal transition and migrate
- Neural crest cells give rise to:
 - Dorsal root ganglia
 - Enteric ganglia
 - Schwann cells
 - Melanocytes
 - Parasympathetic and sympathetic ganglia
 - Muscle, cartilage and bone of the skull, face, jaw, pharynx and dentine



Segmentation of the Neural Tube

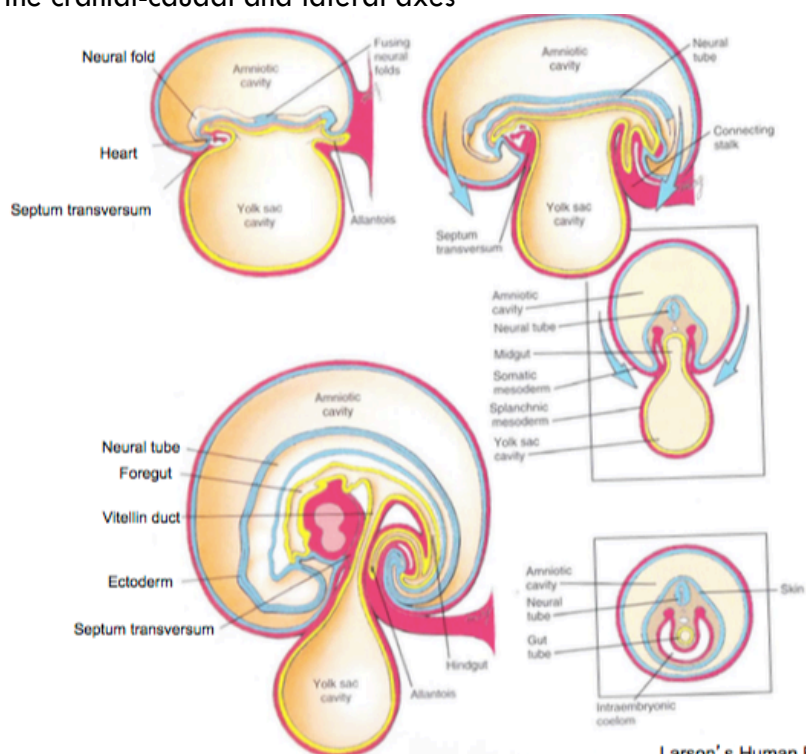
- Cranial end of the neural tube forms vesicles, which gives rise to the brain
- Remainder forms the spinal cord
- The patterning of this segmentation is regulated by Hox genes:
 - Order and location of gene/s on the chromosome predicts the pattern of expression in the embryo
 - Areas of the CNS where the gene is expressed corresponds to its location on the chromosome

Development of Skin

- Epidermis arises from ectoderm that is colonized by melanocytes (neural crest cells) and Langerhans cells (immune cells from bone marrow)
- Dermis in the face arises from neural crest cells too, and therefore is ectodermal

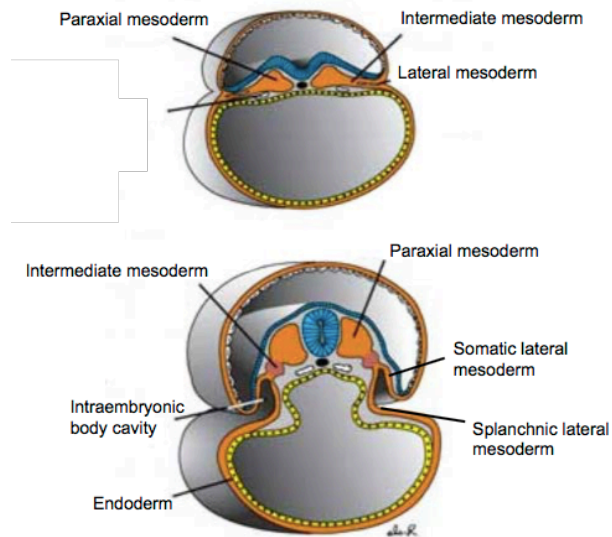
BODY FOLDING

- Embryo growth is rapid, especially in length
- Folding initiates to generate body form
- Driven by different growth rates (embryonic disc and amnion grow faster than the yolk sac)
- Folding occurs in the cranial-caudal and lateral axes



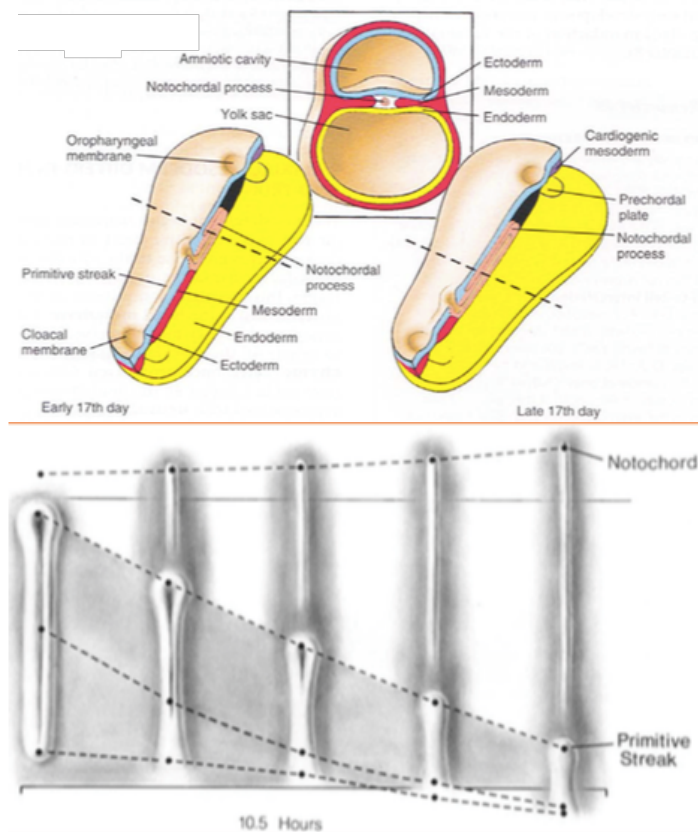
MESODERM

Mesoderm differentiates through body folding.



Notochord

- Cartilage-like transient structure
- Important for the induction of other organs (e.g. neural tube)
- Cranial-midline extension of the primitive node to form a hollow tube
- Tube grows in length as cells are added from the primitive node
- Primitive streak regresses as the notochord grows (if it doesn't regress, it causes teratomas)

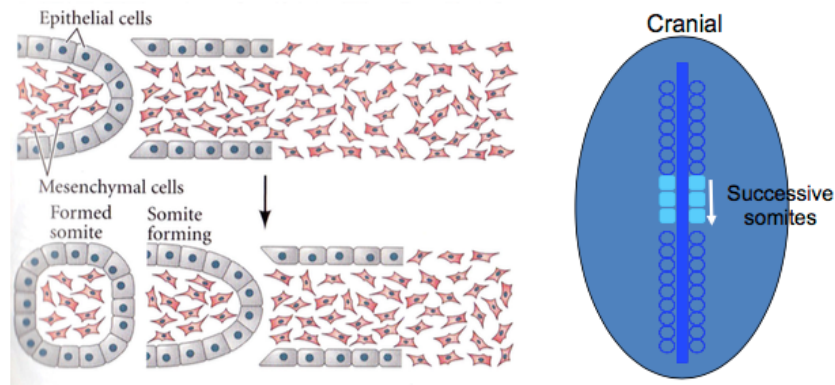


Paraxial Mesoderm

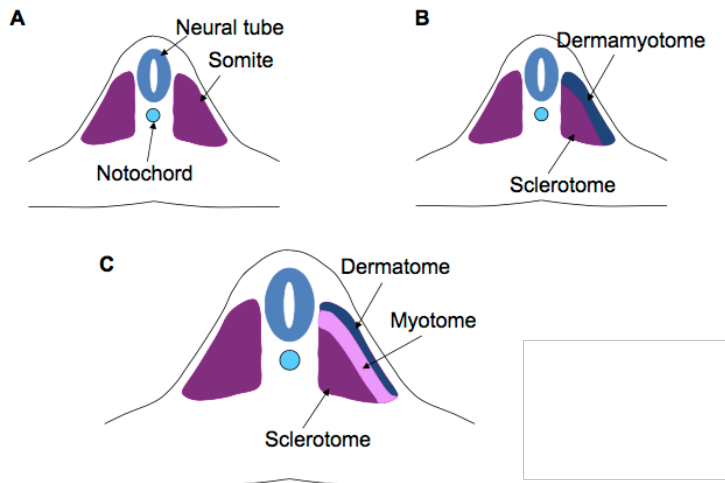
- Located closest to the neural tube
- Differentiates into different cells in the head vs in the trunk
- In the head, paraxial mesoderm along with neural crest cells form the bone, muscle and connective tissue of the face and skull
- In the trunk, paraxial mesoderm forms somites, which gives rise to dermis, muscle and bone

Somitogenesis

- Occurs through a mesenchymal → epithelial cell transition
- As mesenchymal cells become more organised epithelial cells, somites fissure and close off
- Occurs in a cranial → caudal direction, in parallel on both sides of the neural tube

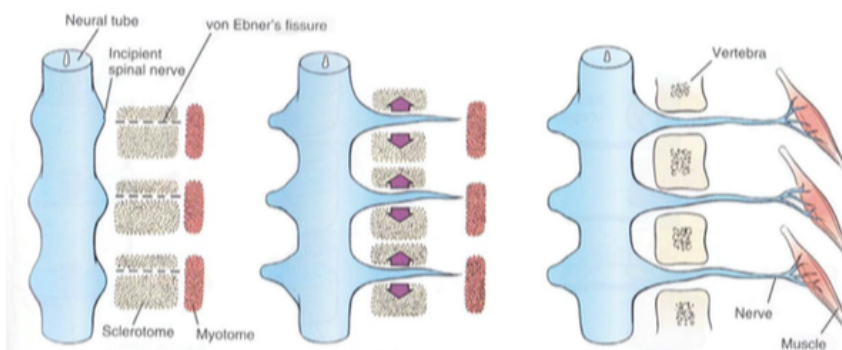


- Somites differentiate into:
 - Epithelial dermamyotomes – which further differentiate into dermatomes (forms dermis) and myotomes (forms muscle)
 - Mesenchymal sclerotomes
 - Undergoes a epithelial → mesenchymal transition
 - Forms the skeletal elements of the trunk
- This differentiation is driven by Hox genes



Formation of Vertebrae

- Each sclerotome splits into cranial and caudal sections (essentially in half)
- Spinal nerves grow through to innervate myotomes and dermatomes
- Caudal section of one sclerotome fuses with the cranial section of the below sclerotome to form a vertebra



Limb Formation

- Limbs grow from somites
- Form at 'limb fields' and bud off

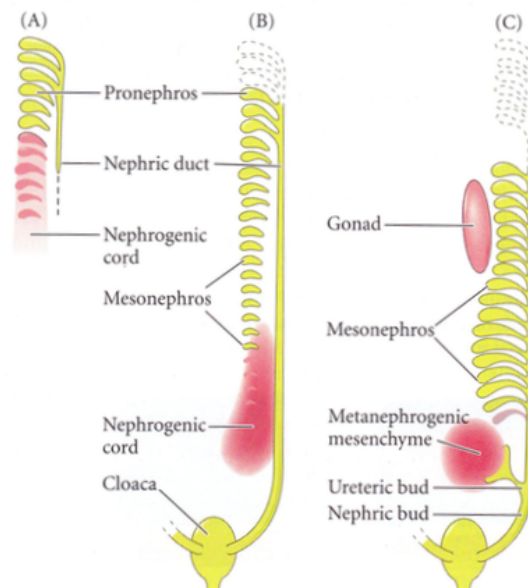
- Mesenchymal cells from lateral plate mesoderm and somites migrate in towards these limb fields
- LP mesoderm forms the skeletal elements of the limb, while somites form the muscle and dermis of the limb
- Limb segmentation is driven by Hox genes
- Digit formation = hands and feet start off as paddles, and digits are sculpted by apoptosis

Intermediate Mesoderm

- Located between lateral plate and paraxial mesoderm
- Forms the urogenital system (kidneys, gonads and associated ducts)

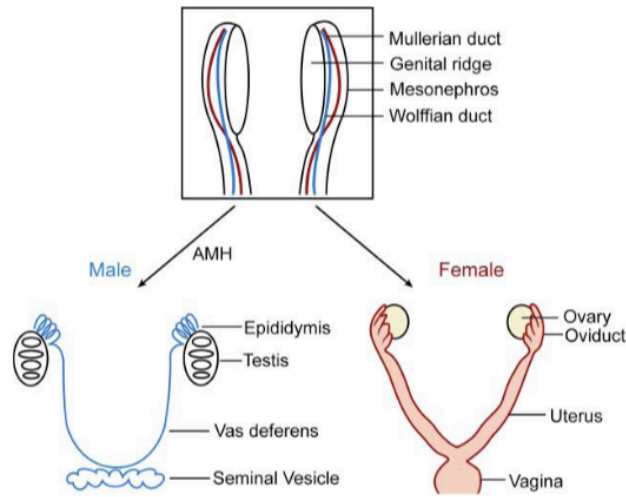
Kidneys

- Nephric duct (Wolffian Duct) forms in the mesoderm
- At the cranial end, tubules form (pronephros) which connect to the nephric duct, but quickly deteriorate
- At the caudal end:
 - Tubules form (mesonephros) which acts as the embryonic kidney
 - Bud forms out of the nephric duct (uretric bud) which gives rise to the ureter
- The end of the uretric bud fuses with metanephric mesenchyme to form the kidney



Gonads

- Form at the nephric duct from thickening of the surface of the mesonephros
- Gonads develop as the genital ridge, which is a bipotential precursor (can differentiate into ovaries or testes)
- SRY gene on the Y chromosome drive differentiation of the gonads into testes
- Lack of SRY gene (due to no Y chromosome) causes differentiation into ovaries
- Genital tracts run parallel to the mesonephros
- All embryos have Wolffian and Mullerian Ducts
- If the gonads → testes, testosterone and antimullerian hormone (AMH) cause degeneration of the Mullerian duct, and the Wolffian duct goes on to form the male reproductive tract
- If the gonads → ovaries, the Wolffian duct degenerates due to a lack of testosterone, and the Mullerian duct goes on to form the female reproductive tract



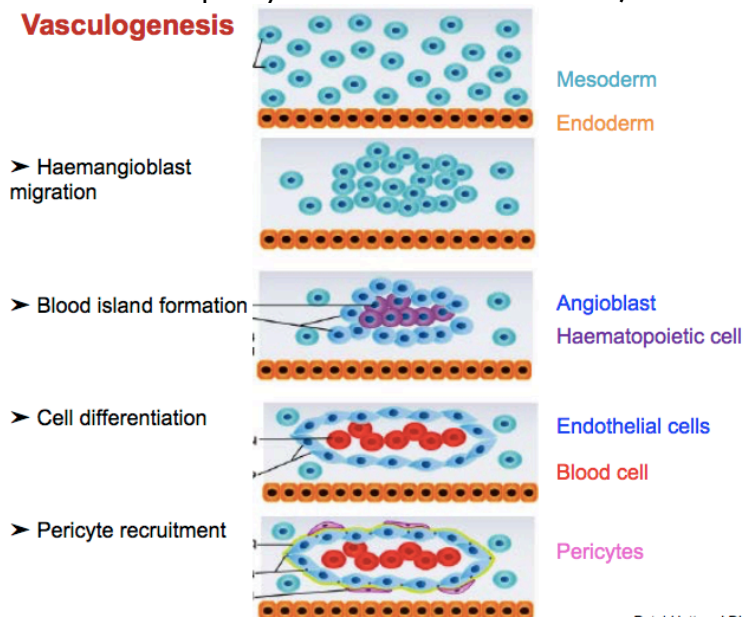
Lateral Plate Mesoderm

- Located furthest from the neural tube
- Divides into somatic and splanchnic LP mesoderm
- Through body folding, splanchnic LP mesoderm is closer to the neural tube than somatic LP mesoderm
- Forms the ventrolateral body wall, heart and vasculature, and the gut wall

Splanchnic LP Mesoderm forms the circulatory system.

Vasculogenesis

- De novo assembly of blood vessels
- Requires recruitment of mesodermal progenitors to endothelial cells, which then are organised into vessels
- Occurs only during embryogenesis
- Steps:
 1. Endoderm signals to mesoderm, causing mesodermal cells to cluster and form haemangioblasts
 2. Haemangioblasts differentiate:
 - Outer cells form angioblasts
 - Inner cells form haematopoietic cells
 3. Haematopoietic cells go on to form blood cells, while angioblasts go on to form endothelial blood vessels
 4. Vessels recruit pericytes that stabilize the vessel, and allow the vessel to contract

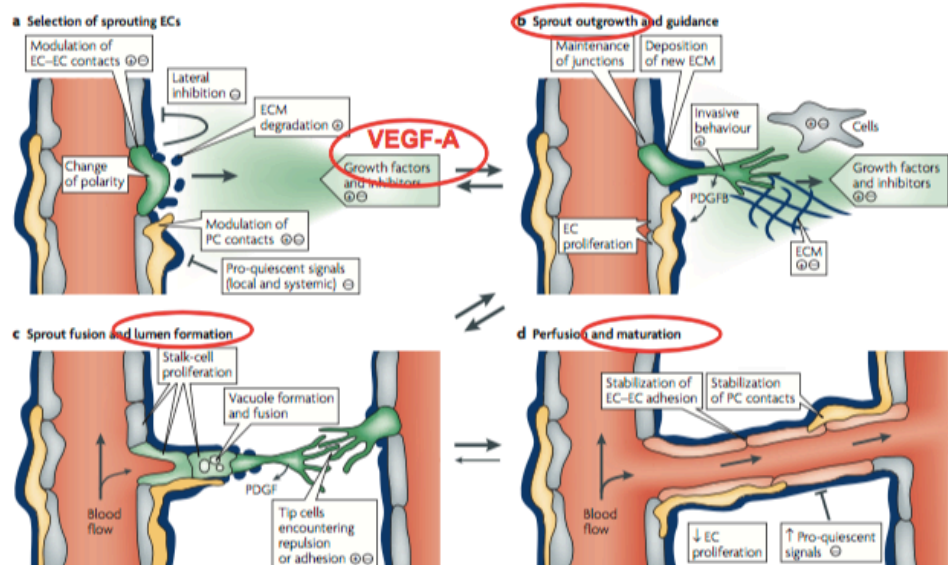


Patel, Hett and D'Ar

Angiogenesis

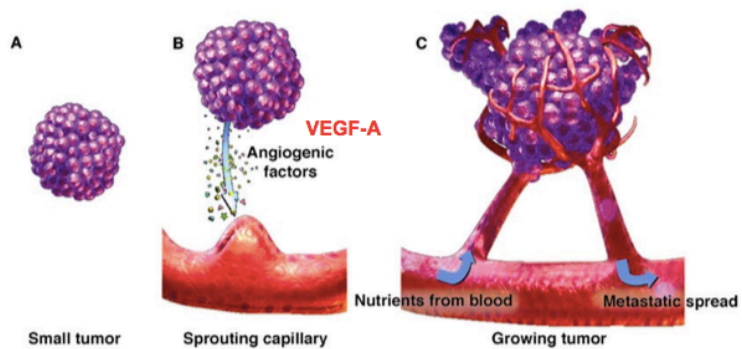
- Blood vessel formation from pre-existing vasculature

- Occurs during embryogenesis and as an adult
- Occurs in a state of hypoxia
- Vessels produce a growth factor (VEGF-A) which causes sprouting of endothelial cells of blood vessels towards the GF
- Sprouts on adjacent vessels fuse and lumen forms
- Pericytes strengthen the vessel

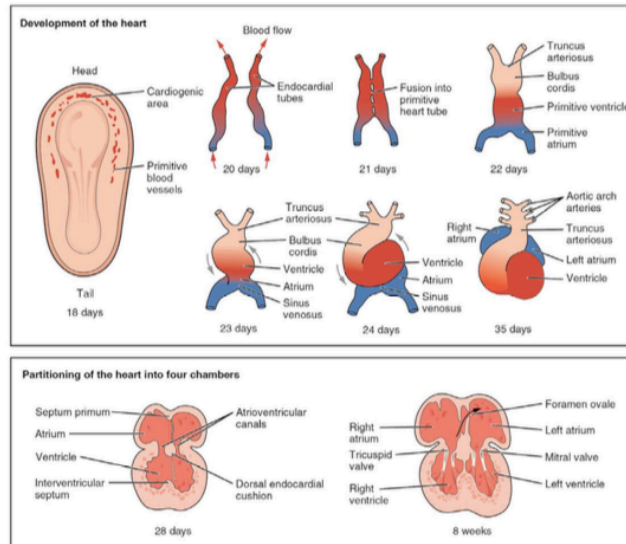


VEGF-A: vascular endothelial growth factor A

- Tumour angiogenesis:
 - When a tumour is too large to survive through diffusion, it will release GF (VEGF-A) causing nearby vessels to sprout
 - Blood vessels provide the tumour with oxygen, and facilitate metastatic spread



- Formation of the heart:
 - Two endocardial tubes fuse in the centre to form the primitive heart tube
 - The tube has 4 vessels leaving it (go on to form the great vessels)
 - Heart tube twists and loops, and septum's form to separate the 4 chambers



Lymphangiogenesis

- Lymphatic system develops from pre-existing veins
- Cardinal veins buds towards a GF (VEGF-C) to form lymph sacs
- Lymph sacs then form their own vascular system

Septum Transversum

- Through body folding, some mesodermal cells move under and inwards, essentially cutting the embryo in half, these cells form the septum transversum
- Septum transversum separates the coelom into thoracic and abdominal cavities, as it develops into part of the diaphragm
- Also forms part of the ventral mesentery of the stomach and duodenum

