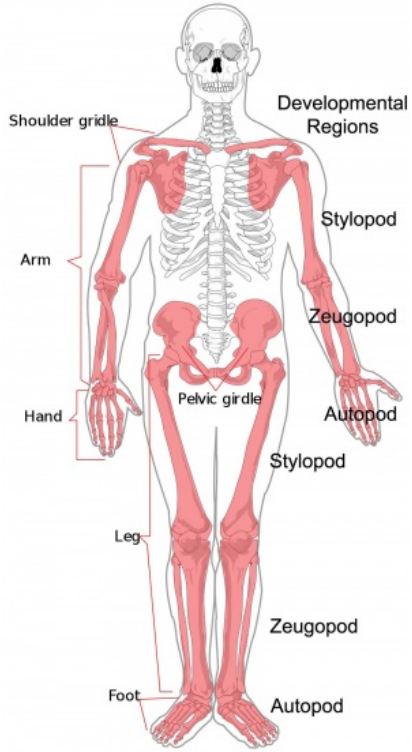
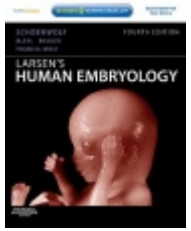
Limb Development





Resources:
http://php.med.unsw.edu.au/embryology/
Larsen's Human Embryology
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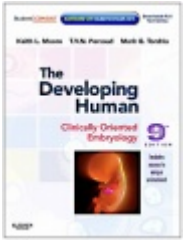

Dr Annemiek Beverdam – School of Medical Sciences, UNSW
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Lecture overview
Limb Development

Embryonic tissues contributing to limb development

Limb axes

Initiation

Proximo-distal outgrowth and patterning

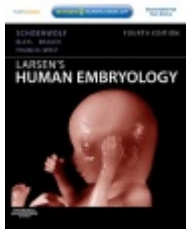
Antero-posterior patterning

Dorso-ventral patterning

Autopod development

Limb skeleton, musculature, innervation, vasculature

Limb rotation



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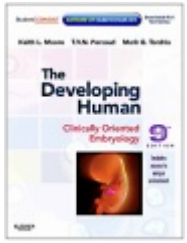

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End product gastrulation:

Trilaminar embryo

Ectoderm *(Neural crest)*
brain, spinal cord, eyes, *peripheral nervous system*
epidermis of skin and associated structures,
melanocytes, cranial connective tissues (dermis)

Mesoderm
musculo-skeletal system, limbs,
connective tissue of skin, organs and cranium,
urogenital system, heart, blood cells

Endoderm
epithelial linings of gastrointestinal, liver, pancreas,
thyroid and respiratory tracts

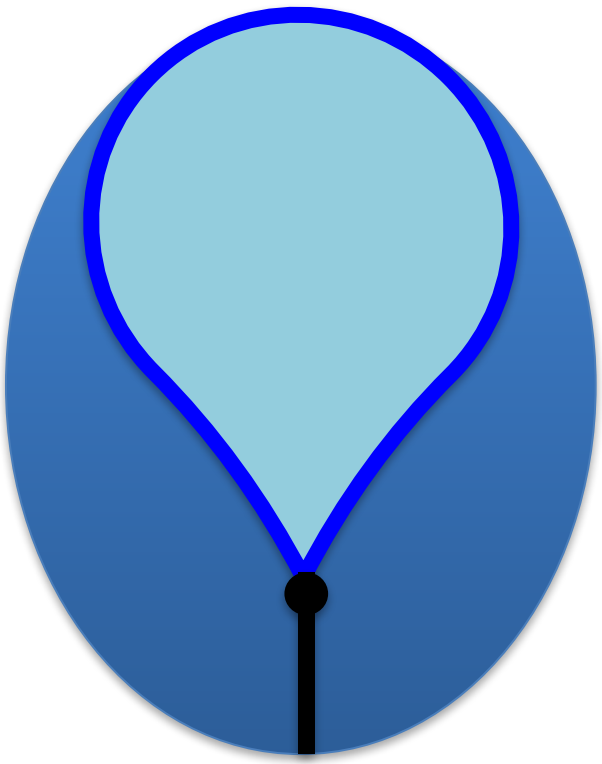
Embryonic tissues contributing to limb development

Lateral ectoderm
Lateral Plate Mesoderm
Paraxial Mesoderm

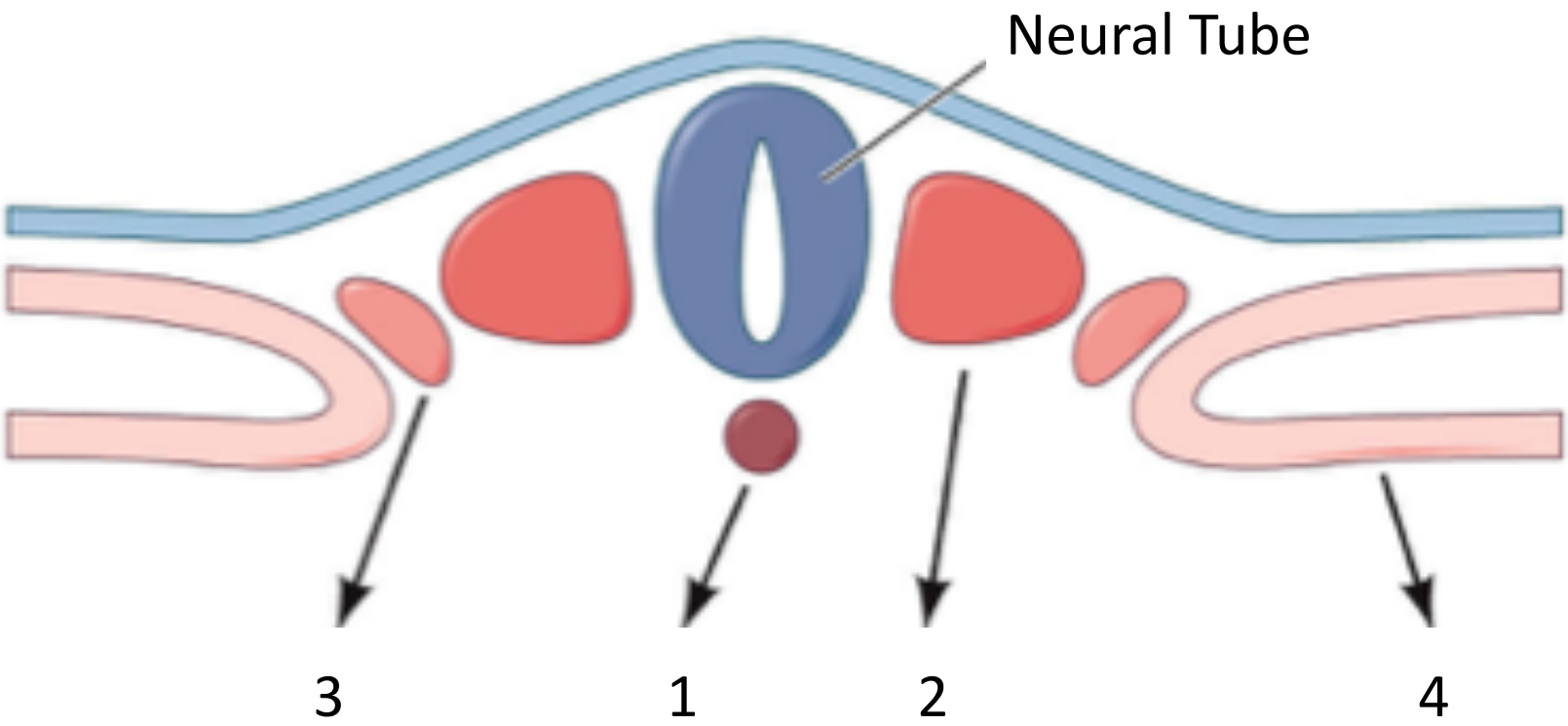
Week 4 embryo

Embryonic tissues contributing to limb development

Lateral Ectoderm

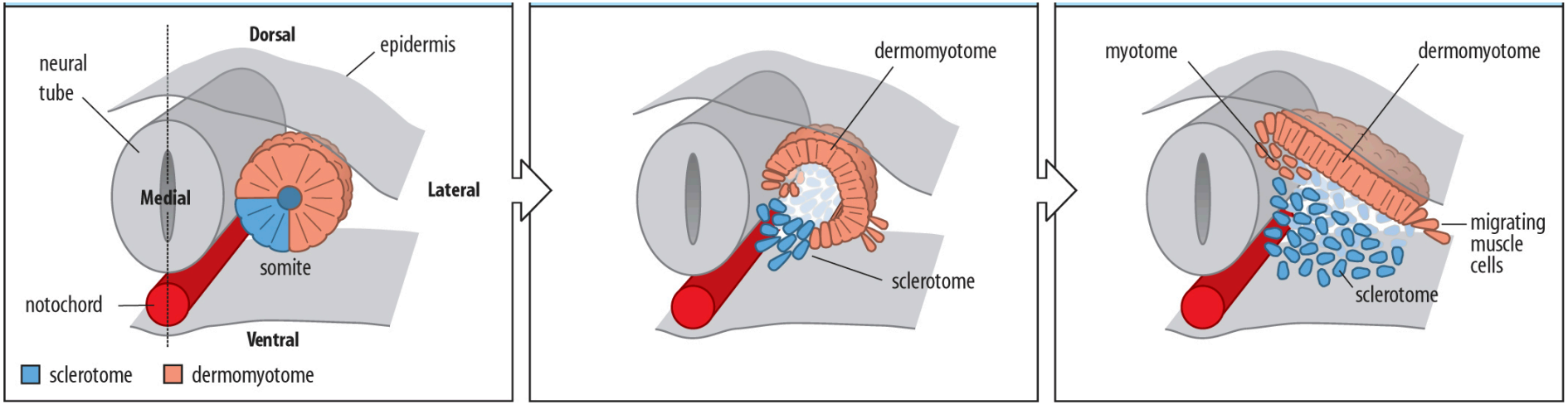


Embryonic tissues contributing to limb development



1: notochord
2: paraxial mesoderm
3: intermediate mesoderm
4: lateral plate mesoderm

Embryonic tissues contributing to limb development



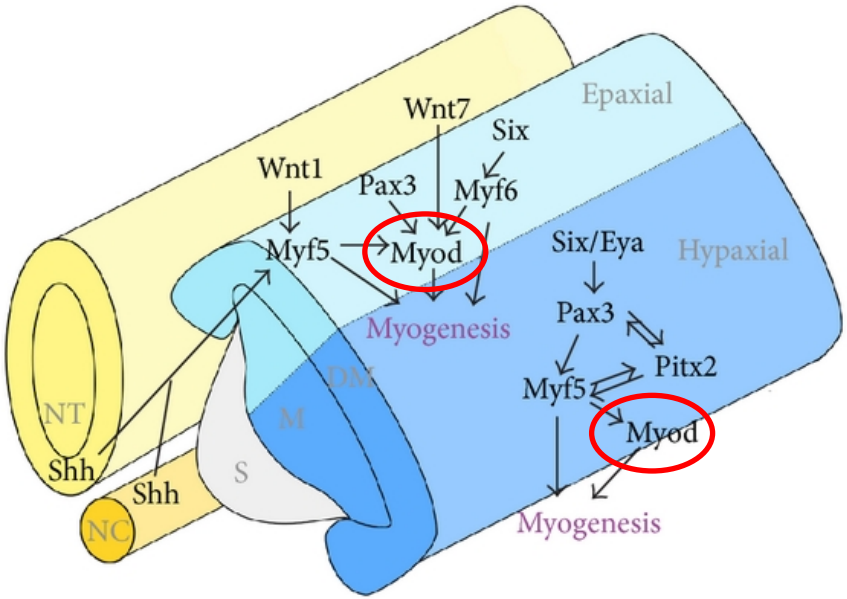
Somites develop into:

- Sclerotome: mesenchymal cells (vertebral body and intervertebral disk)
- Dermomyotome: columnar epithelium

Dermomyotome develops into:

- Dermatome: dermis of the trunk
- Myotome: trunk musculature

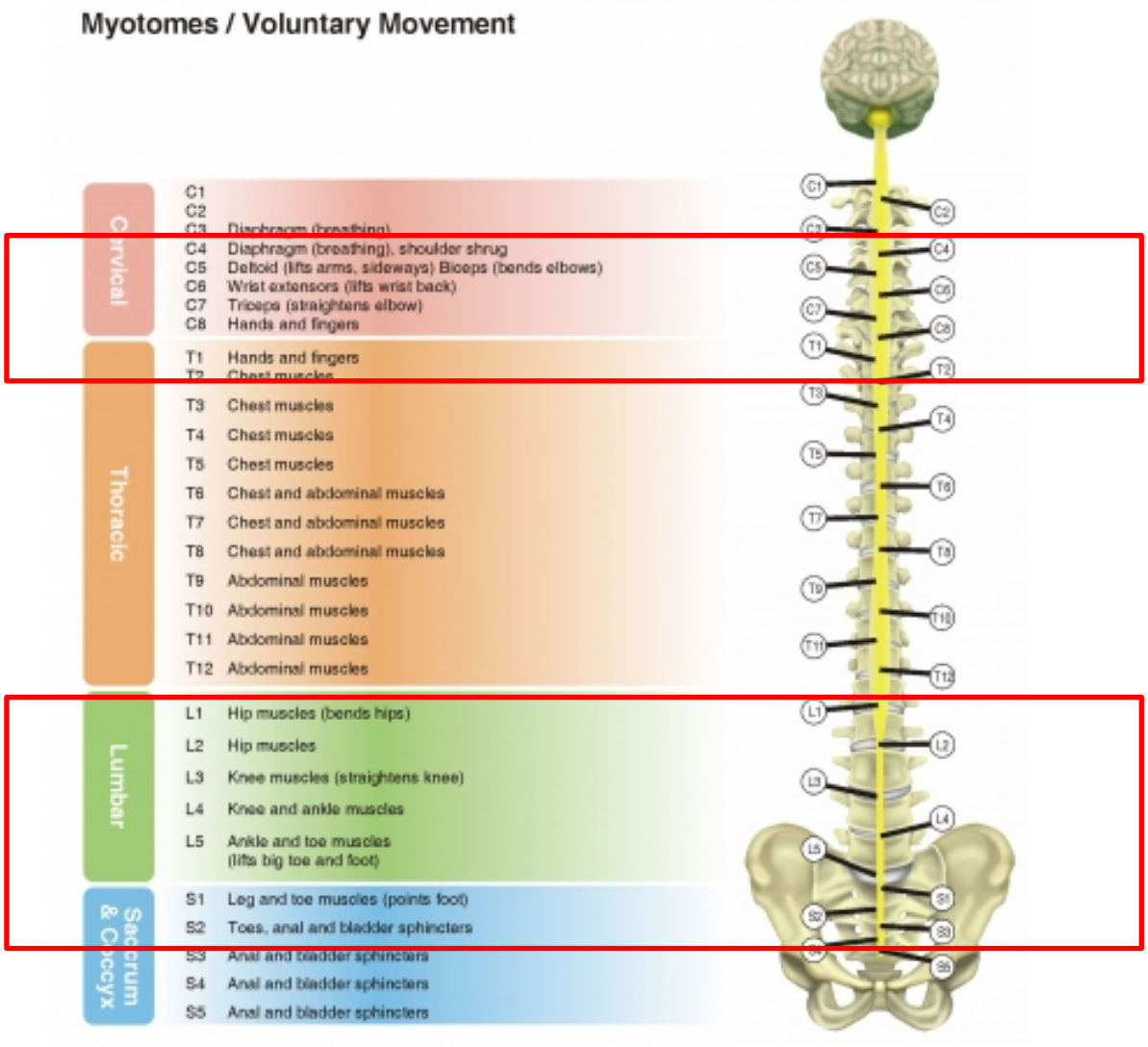
Embryonic tissues contributing to limb development



(a)

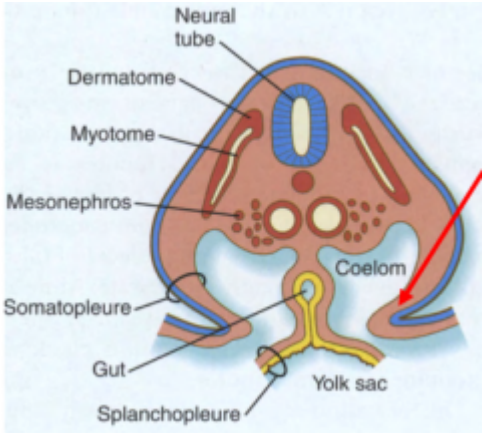
Epaxial myotome: epimere: erector spinae (muscles of the deep back)
Hypaxial myotome: hypomere: 3 primary muscle layers (body wall, limbs)
MyoD initiates myogenesis

Embryonic tissues contributing to limb development

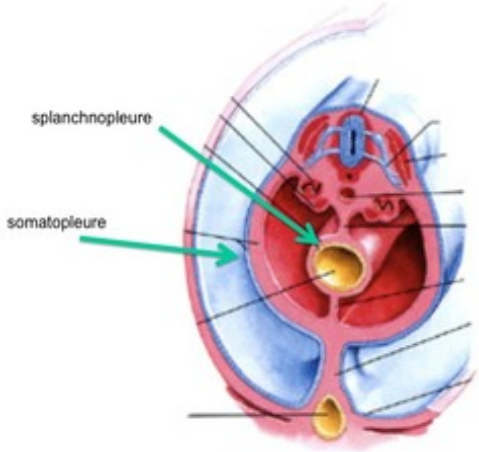


Embryonic tissues contributing to limb development

Somatic/parietal mesoderm: **somatopleure**
- Closest to ectoderm
- Gives rise to:
  - Connective tissue and lining of the body wall
  - Bones, ligaments and dermis of the limbs

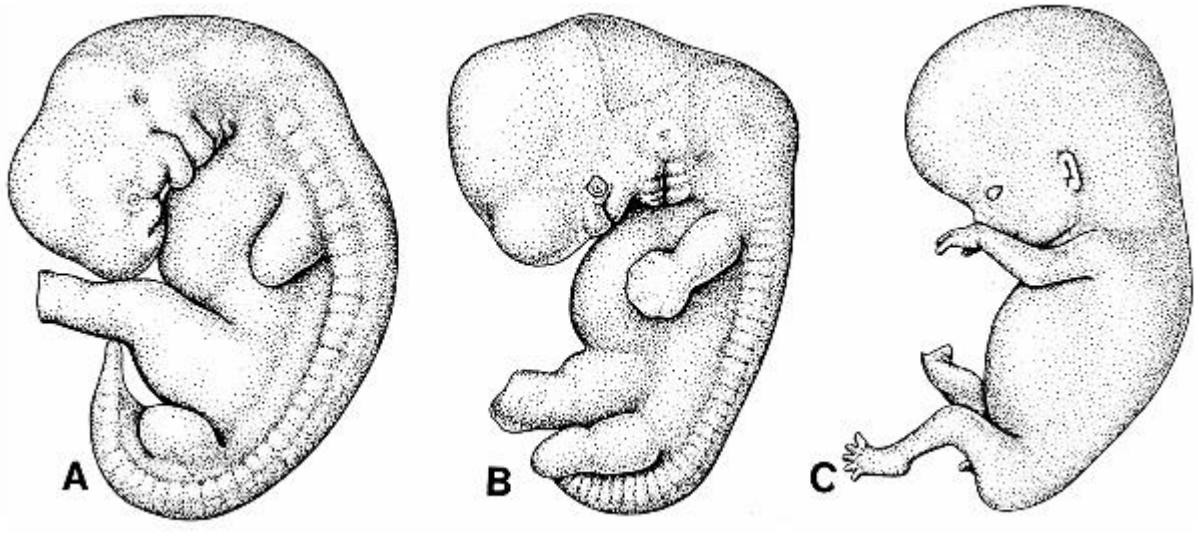


Splanchnic/visceral mesoderm: **splanchnopleure**
- Closest to endoderm
- Gives rise to:
  - Cardiac mesoderm (prechordal splanchnic mesoderm)
  - Blood vessels
  - Smooth muscles of the gut



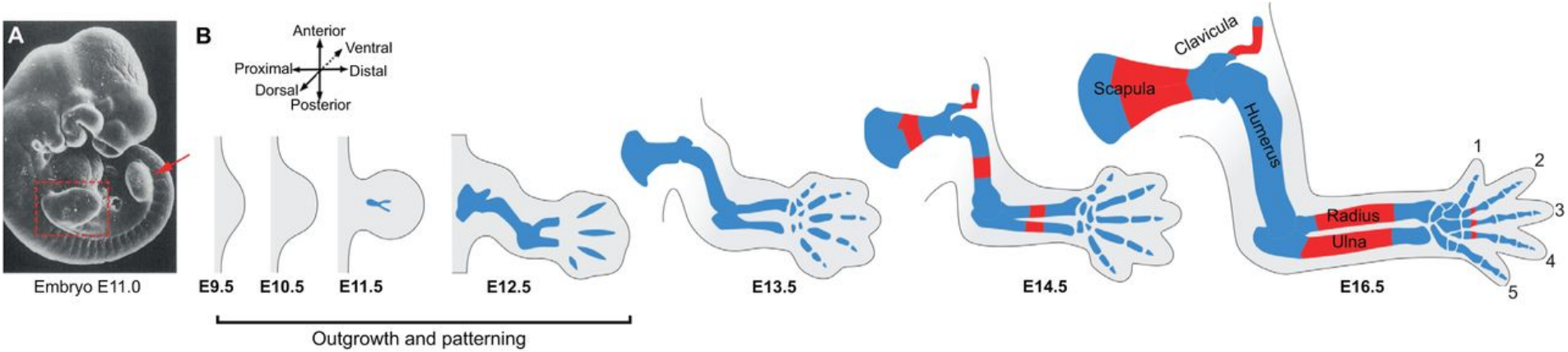
Limb Development

From week 4
Forelimb development ahead of hindlimb development
Proliferation of lateral plate mesoderm
Limb bud: outer ectodermal cap, inner mesodermal core
Apical Ectodermal Ridge



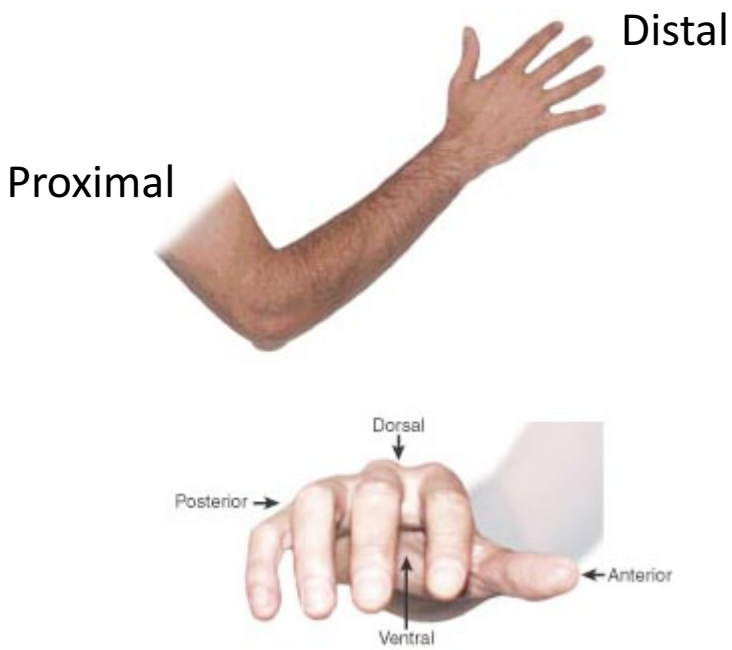
Limb Development

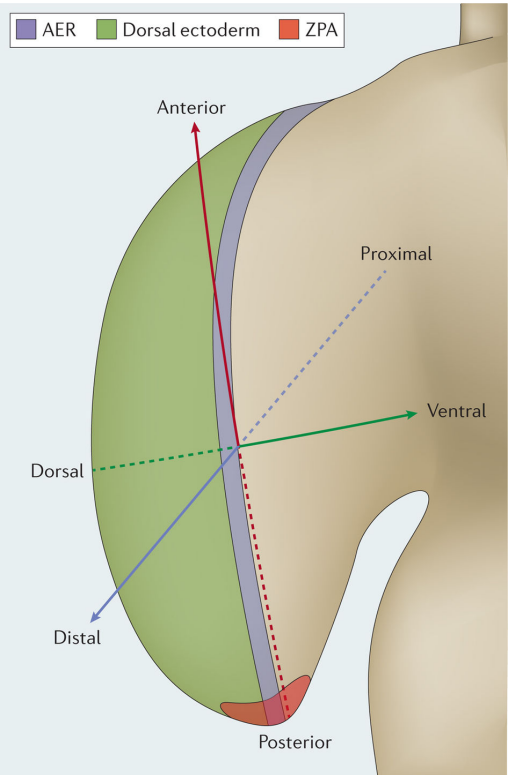
From week 4
Fore limb development ahead of hind limb development
Proliferation of lateral plate mesoderm
Limb bud: outer ectodermally-derived epithelial cap, inner mesodermally-derived core
Apical Ectodermal Ridge



Limb Development
Limb axes

Proximodistal axis
Anteroposterior axis
Dorsoventral axis



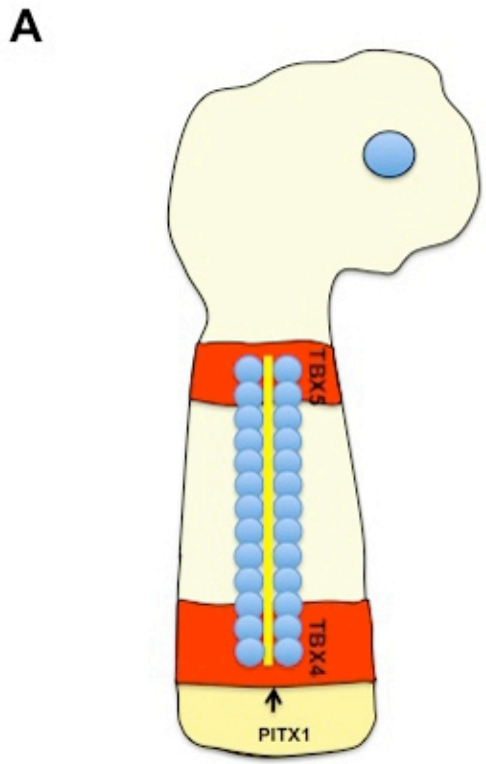


Limb Development
Initiation

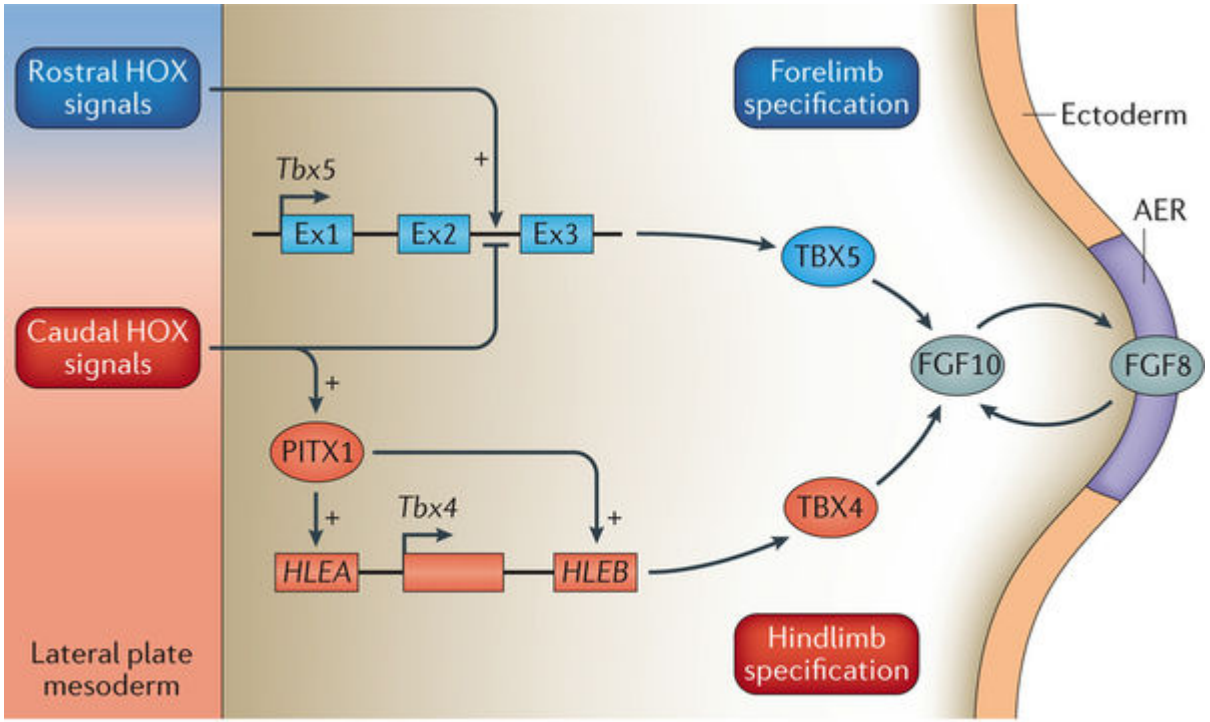
Anterior and posterior limb fields defined by Hox code

Hox -> Tbx4/5

Tbx5 -> FGF10 ⇔ FGF8



Chick wing St. 14
Mouse limb E. 8.0



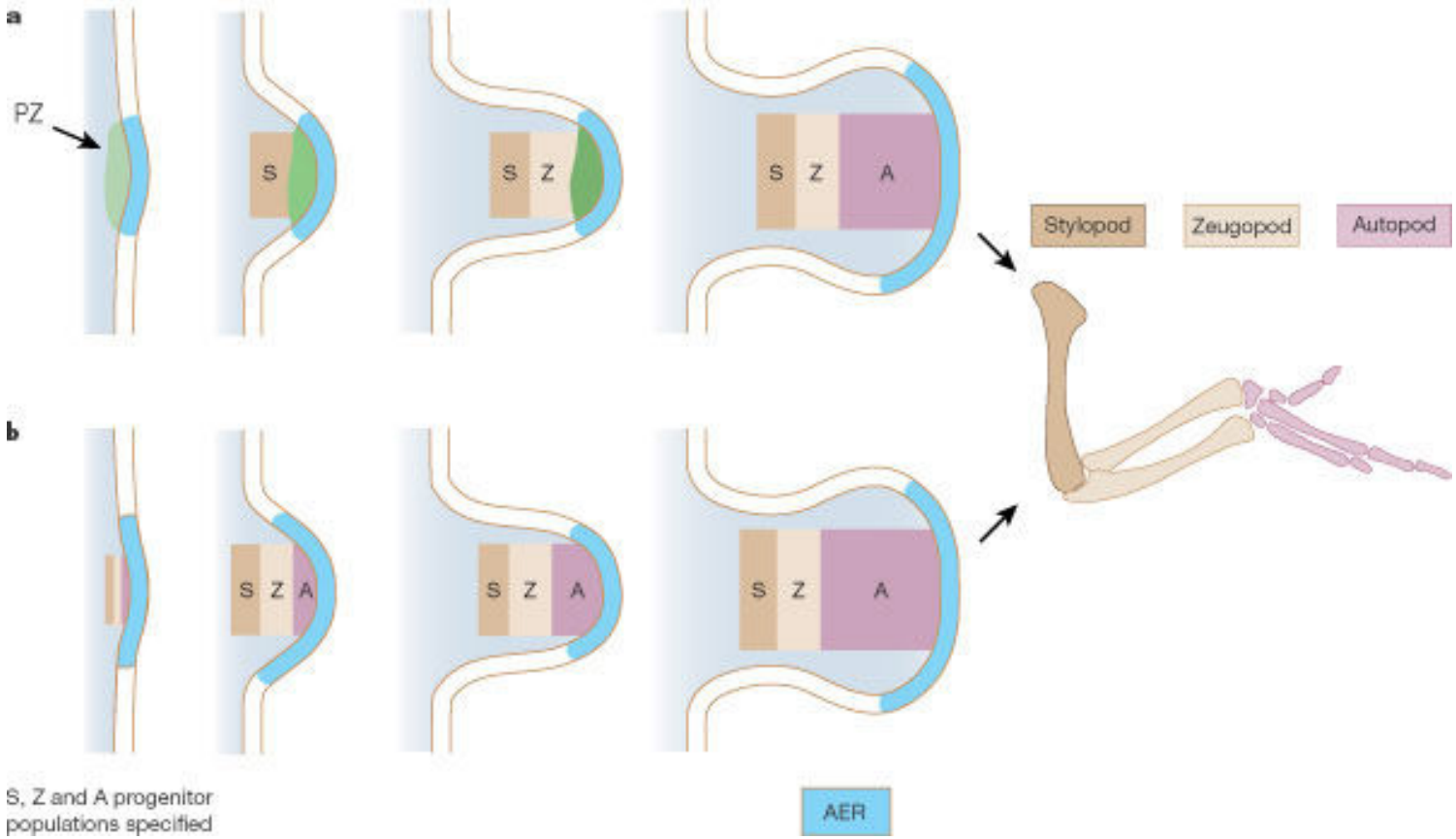
Nature Reviews | Genetics

Limb Development
Proximo-distal outgrowth

FGF10 (mesenchyme) ⇔ FGF8 (AER)
Stylopod, zeugopod, autopod

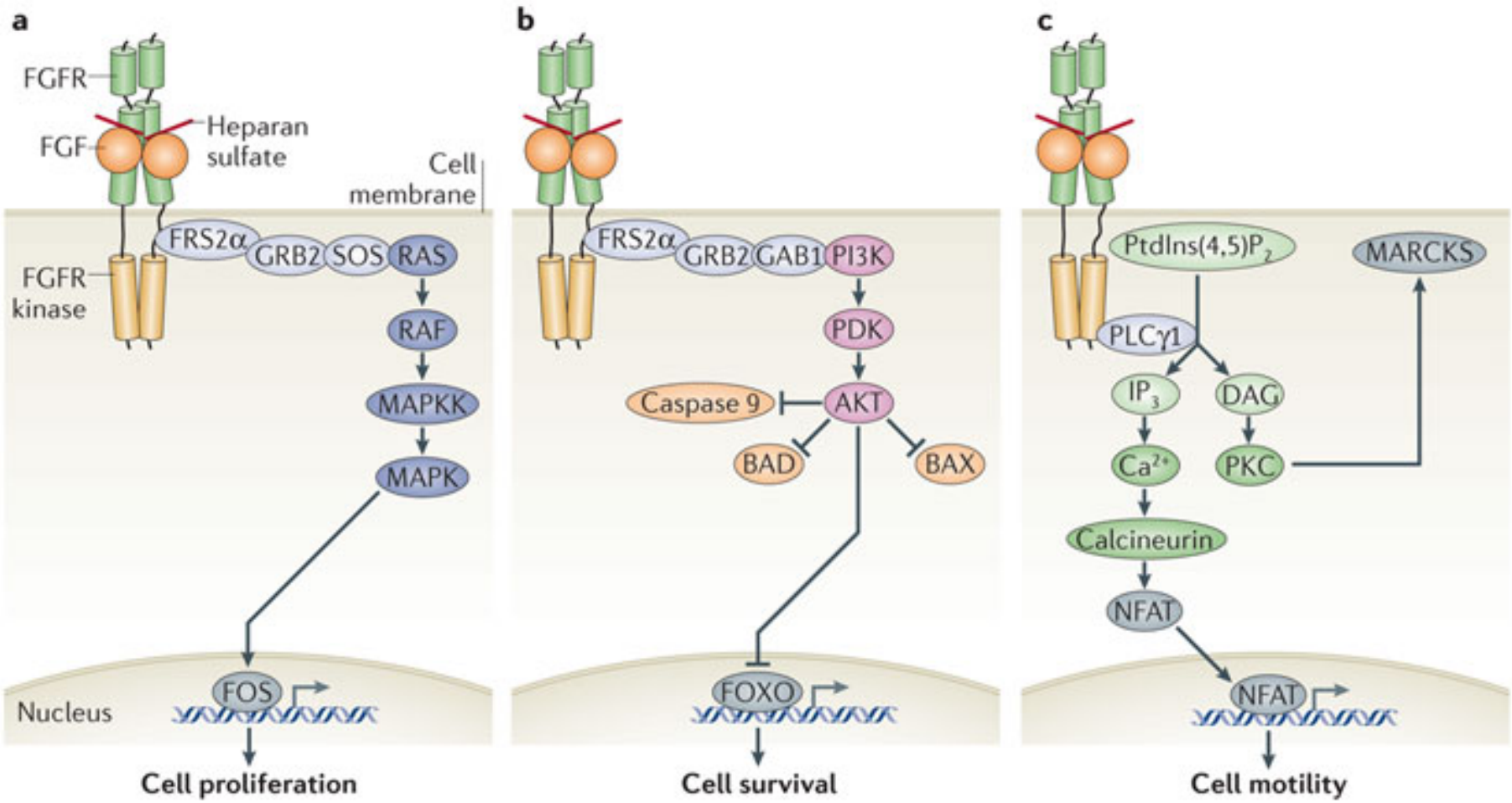
Progress Zone Model

Early Specification Model



Limb Development
Proximo-distal outgrowth

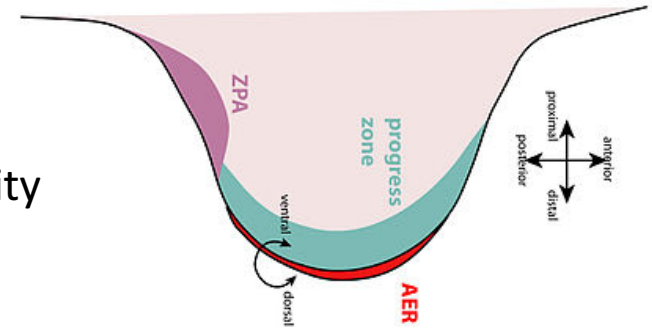
FGF signalling

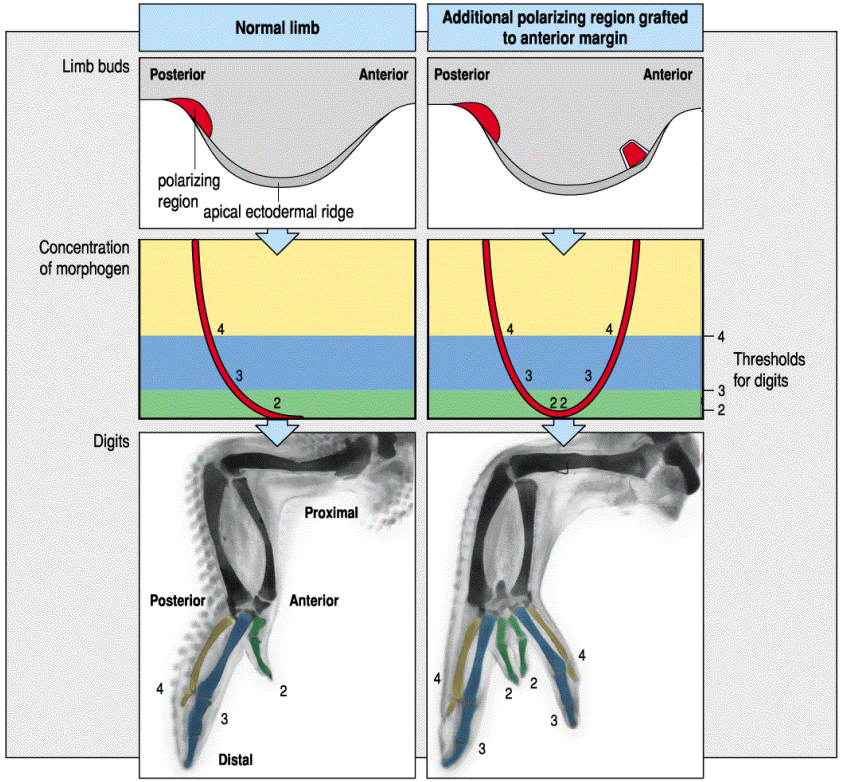


Nature Reviews | Molecular Cell Biology

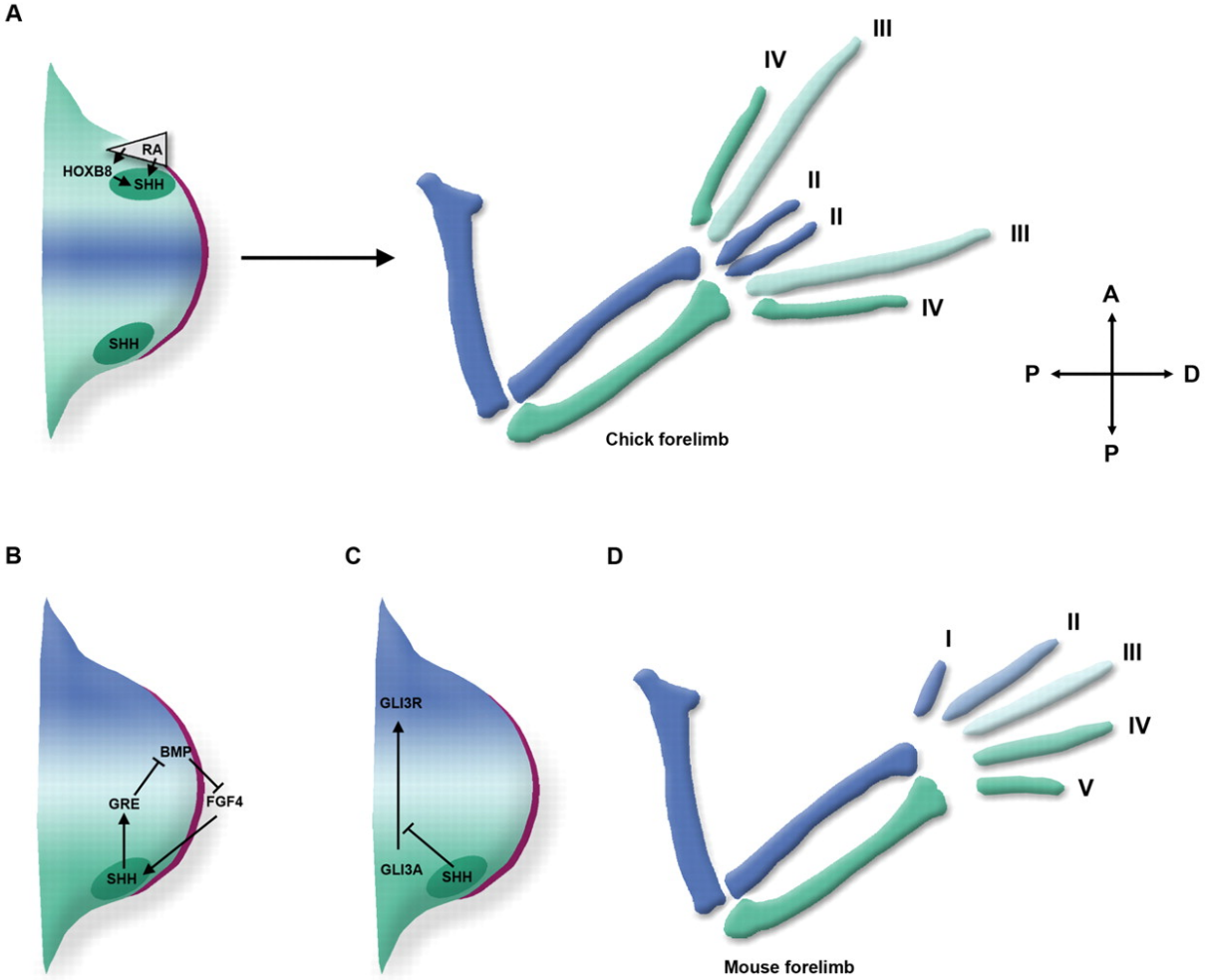
Limb Development
Antero-posterior patterning

ZPA: Zone of polarizing activity





Limb Development
Antero-posterior patterning

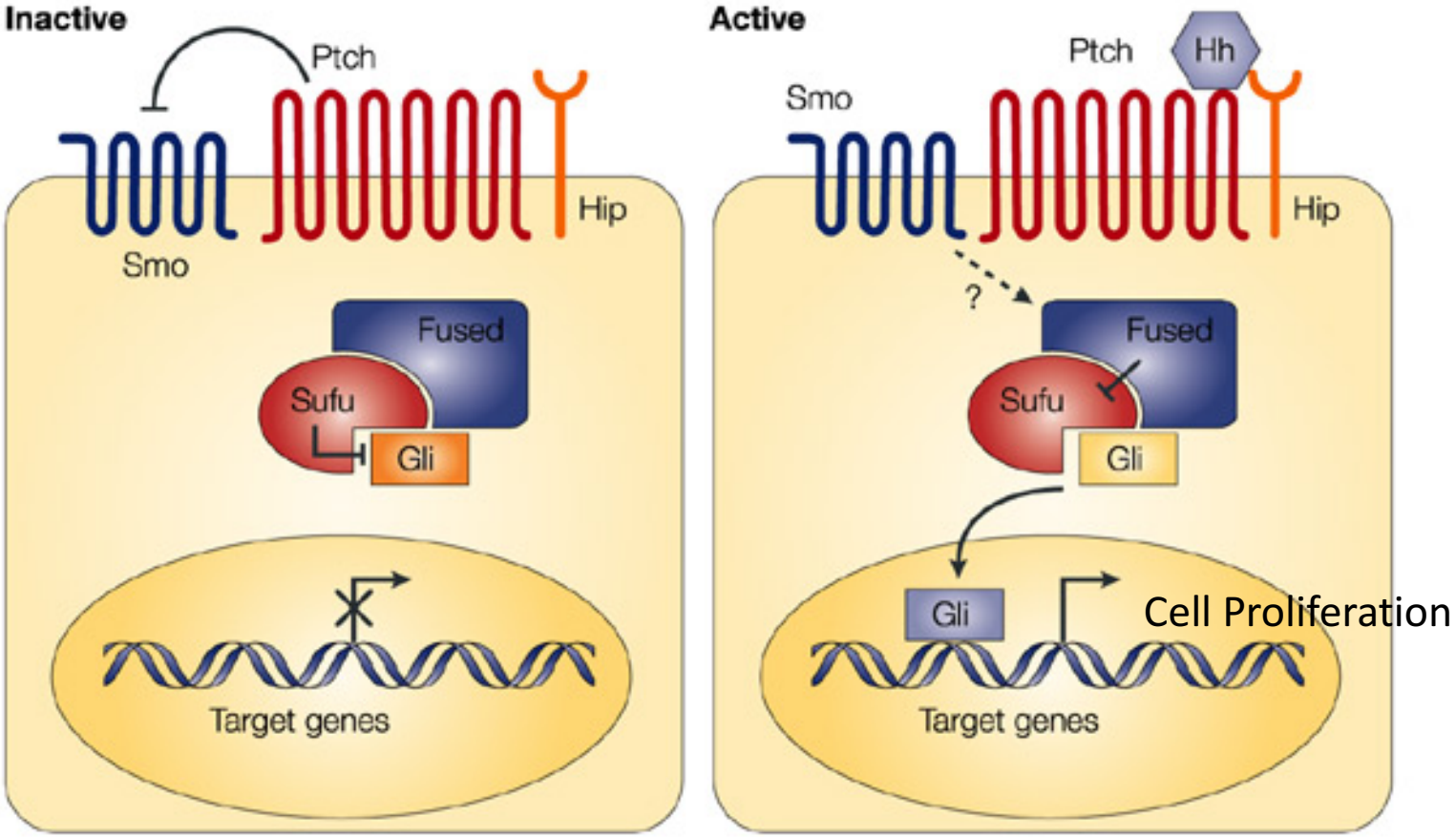


Limb Development
Antero-posterior patterning

Polydactyly

Limb Development
Antero-posterior patterning

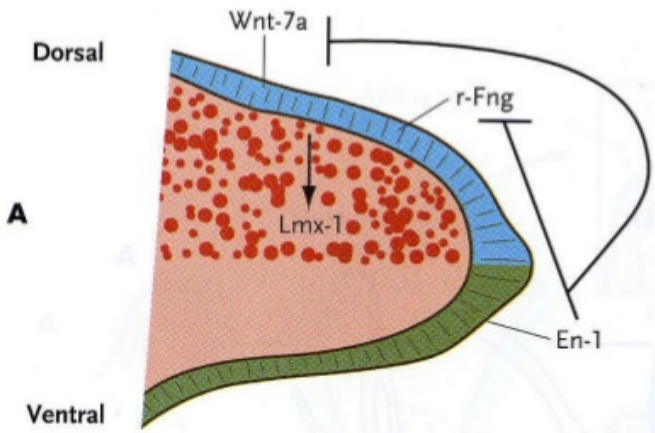
SHH signalling



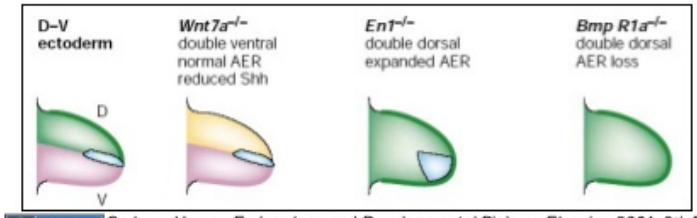
Limb Development
Dorso-ventral patterning

Muscles, tendons dorsally; palms, soles ventrally
Wnt7a (dorsal epithelium) -> Lmx1 (dorsal mesenchyme)

Molecular control of dorsoventral (DV) patterning:



Carlson: Human Embryology and Developmental Biology. Elsevier, 2004. 3rd. Ed.



Carlson: Human Embryology and Developmental Biology. Elsevier, 2004. 3rd. Ed.

Early mesenchymal signals establish *Wnt7a* expression in the dorsal ectoderm and *Lmx1* expression in the dorsal mesenchyme.
- Loss of expression results in bi-ventral limbs.

Expression of *Wnt7a* is restricted to the dorsal ectoderm because it is repressed in the ventral ectoderm by *En1*. *En1* expression is induced by BMP signaling.
-Loss of expression results in bi-dorsal limbs.

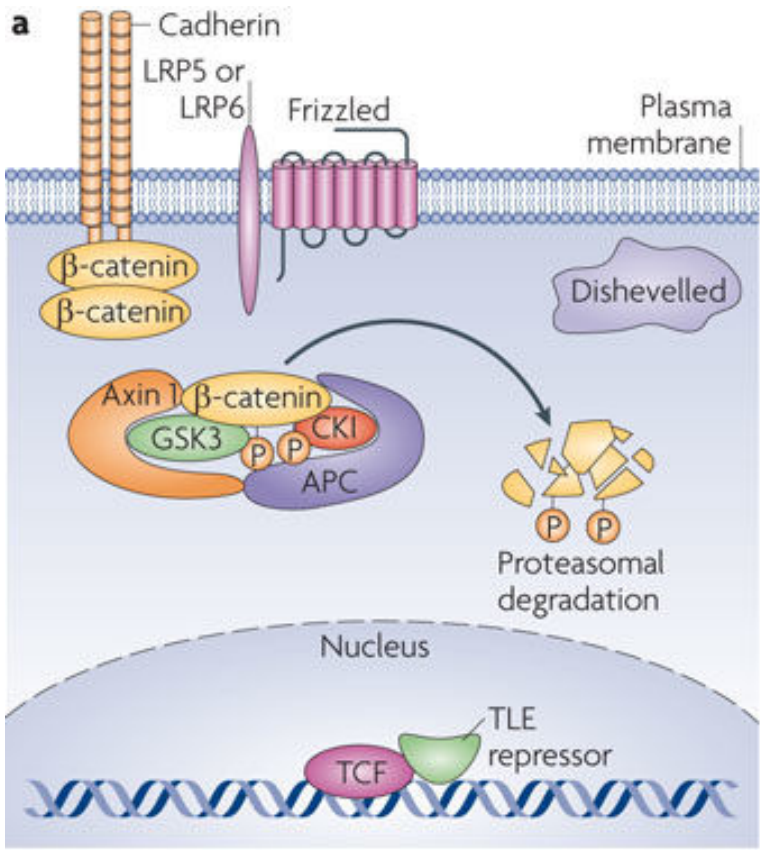
-Important Note: Disruption of DV patterning does NOT affect specification of the skeletal elements.

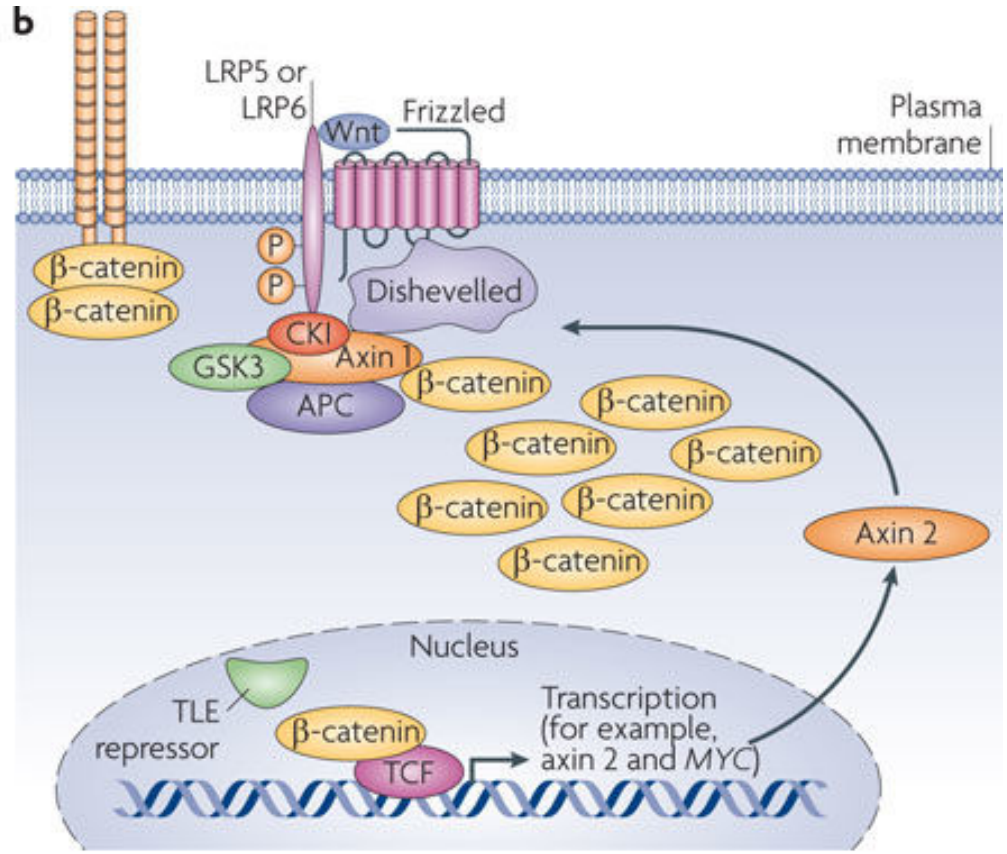
Limb Development
Dorso-ventral patterning

WNT signalling

Inactive

Active



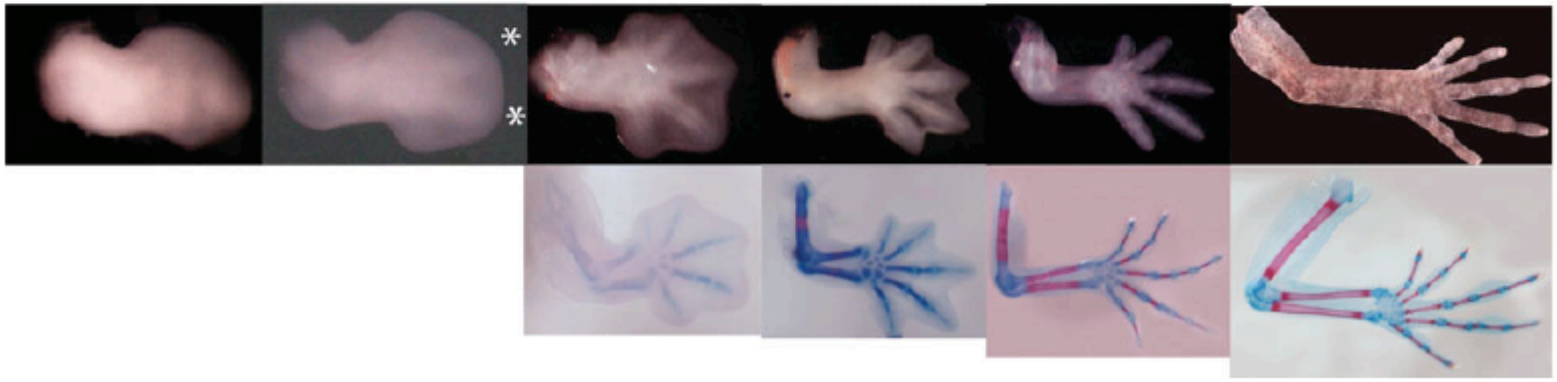


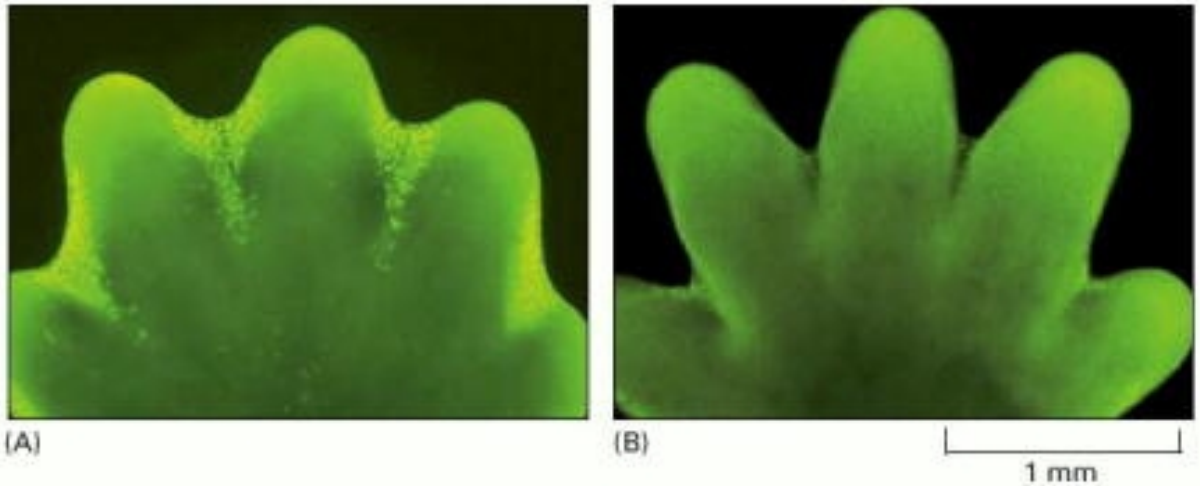
β-catenin acts as adherens junction molecule at the membrane or is degraded

β-catenin acts as transcriptional activator in the nucleus

Limb Development
Autopod development

Interdigital apoptosis

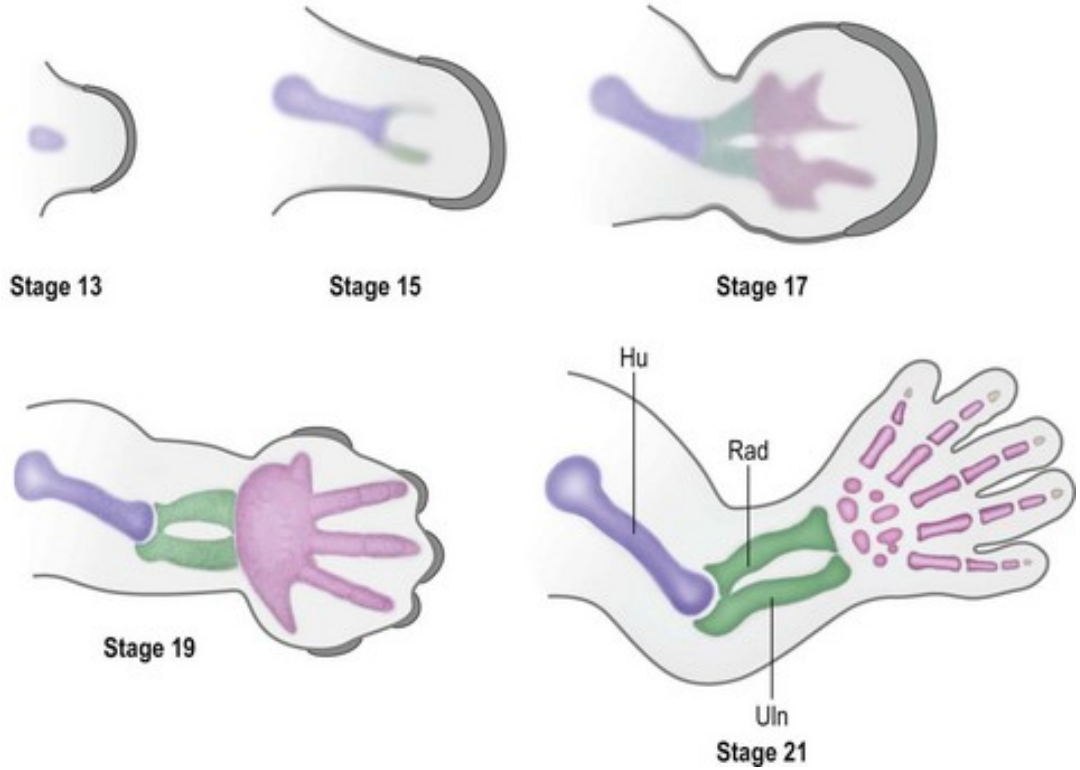


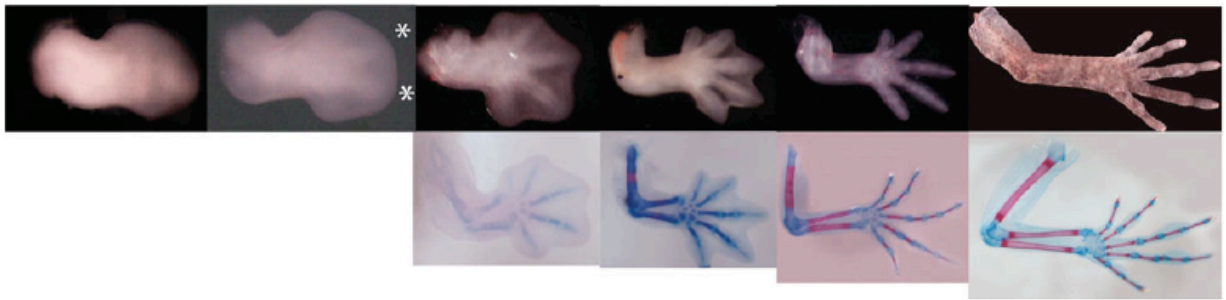


Limb Development
Autopod development

Limb Development
Limb Skeleton

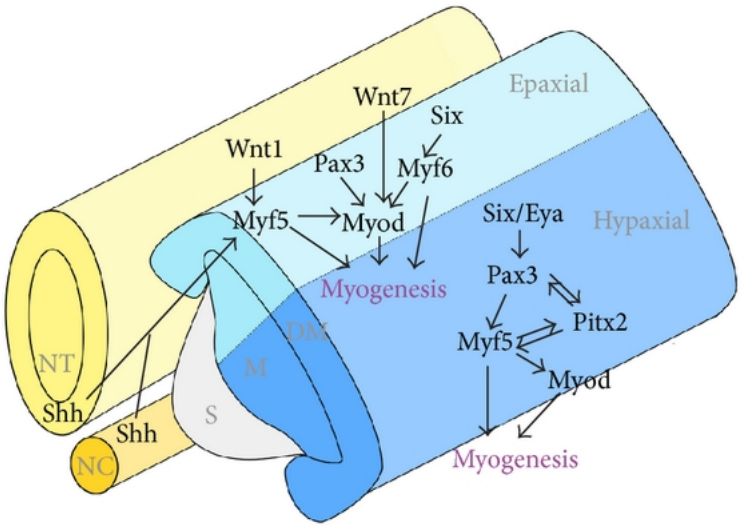
Endochondral ossification



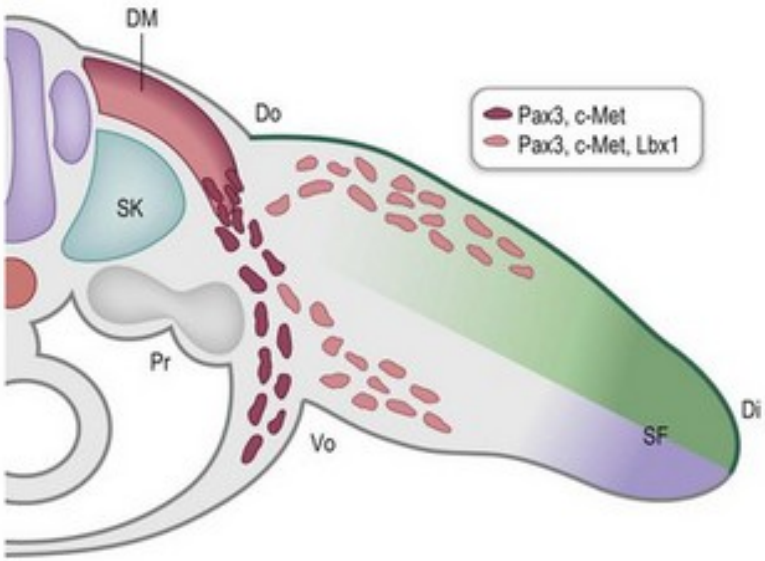


Limb Development
Limb Musculature

Hypaxial myotome

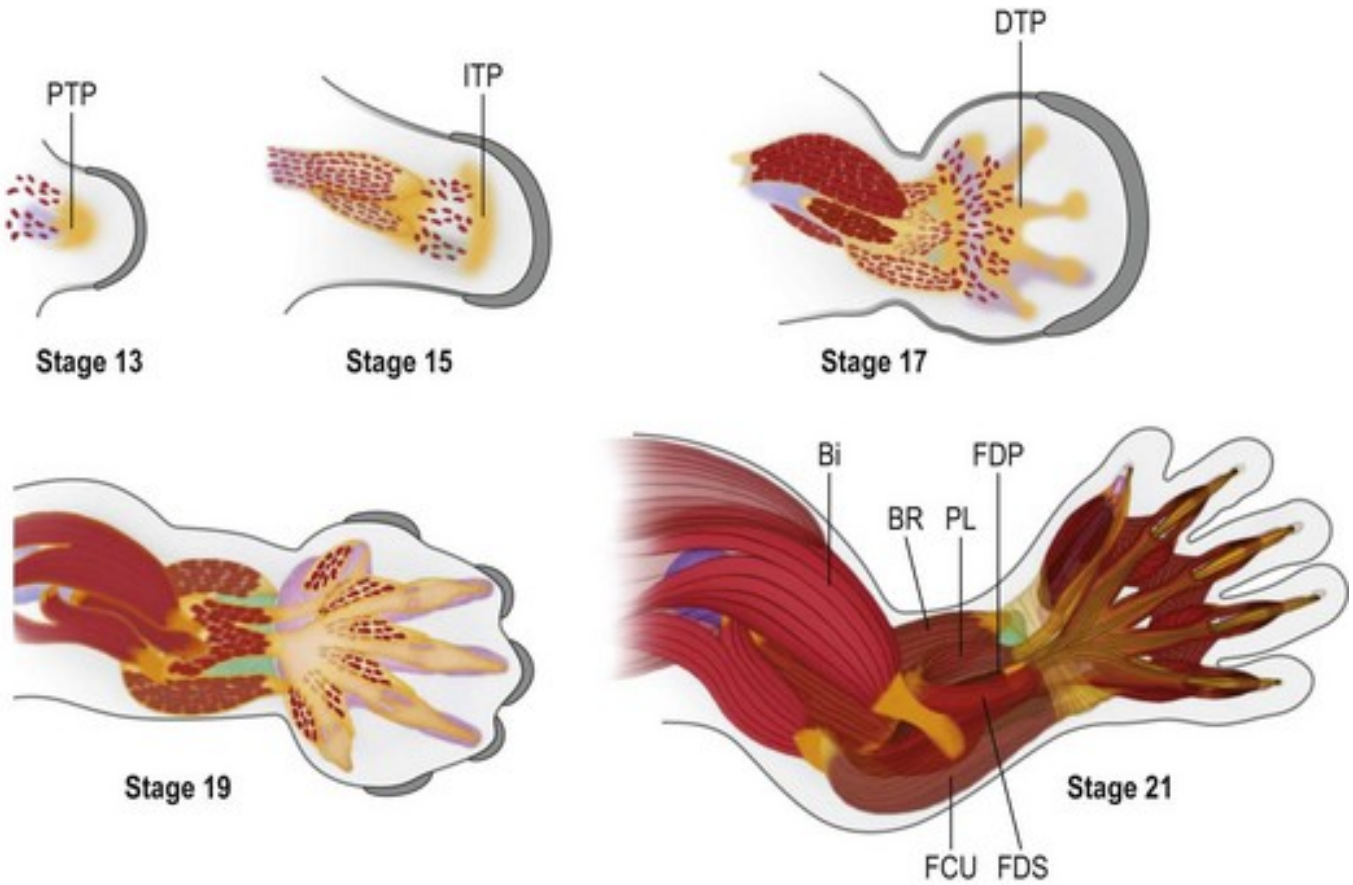


(a)

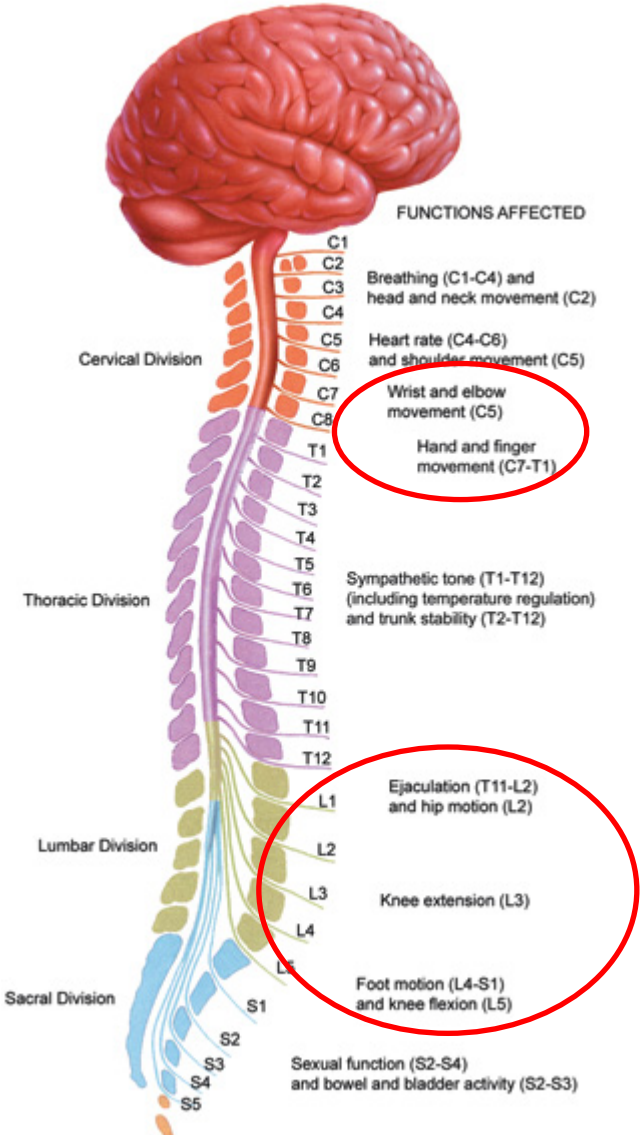


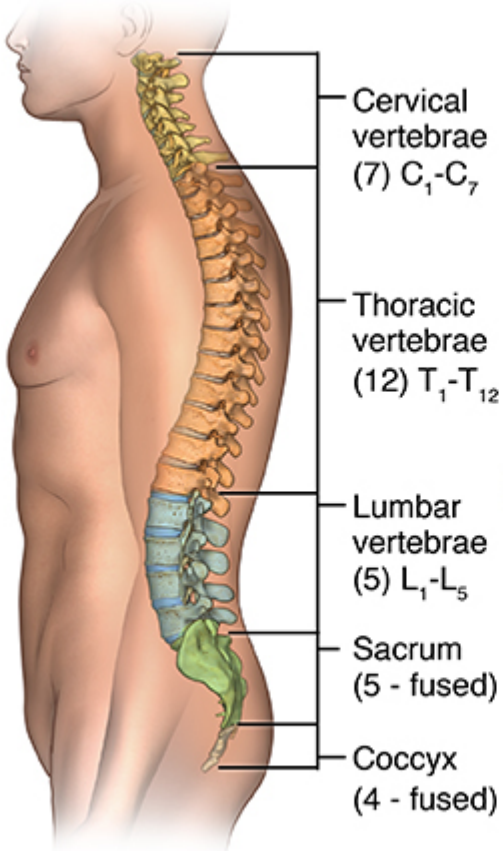
Limb Development
Limb Musculature

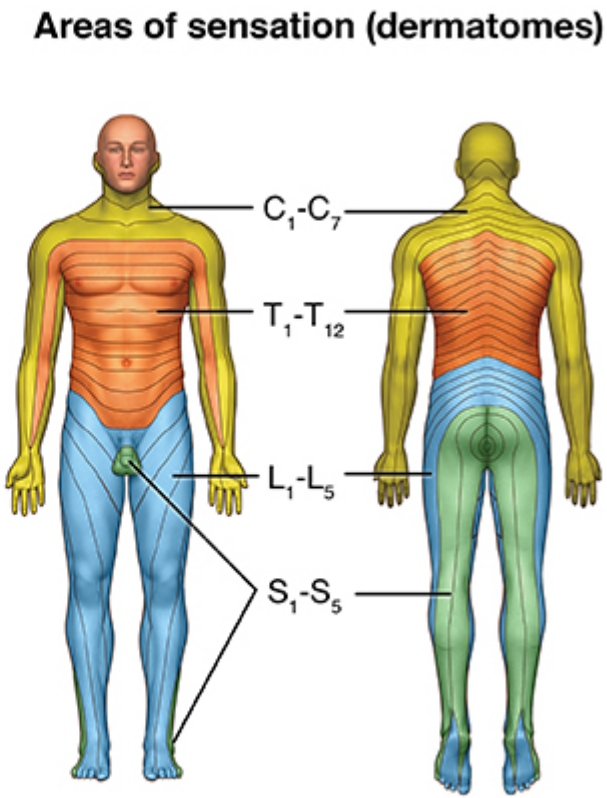
Hypaxial myotome



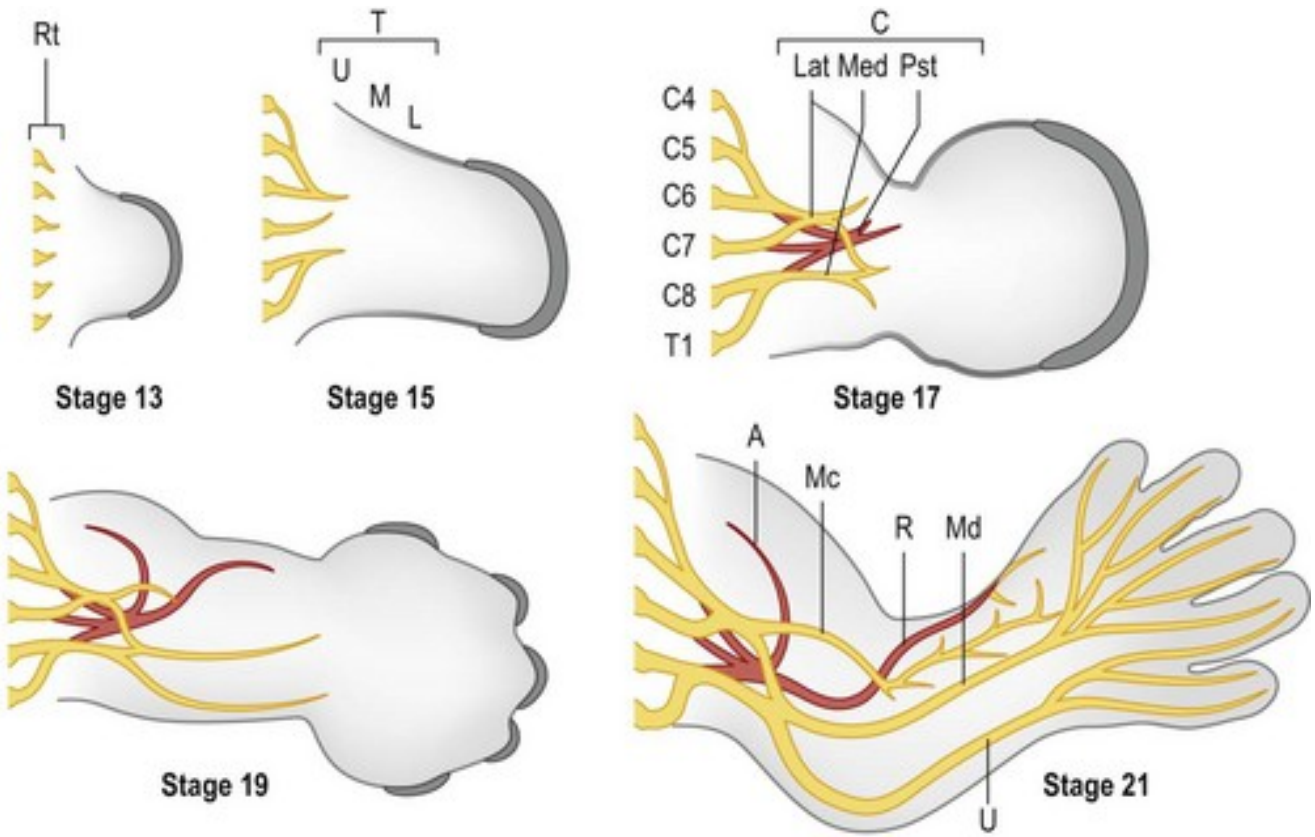
Limb Development
Limb Innervation







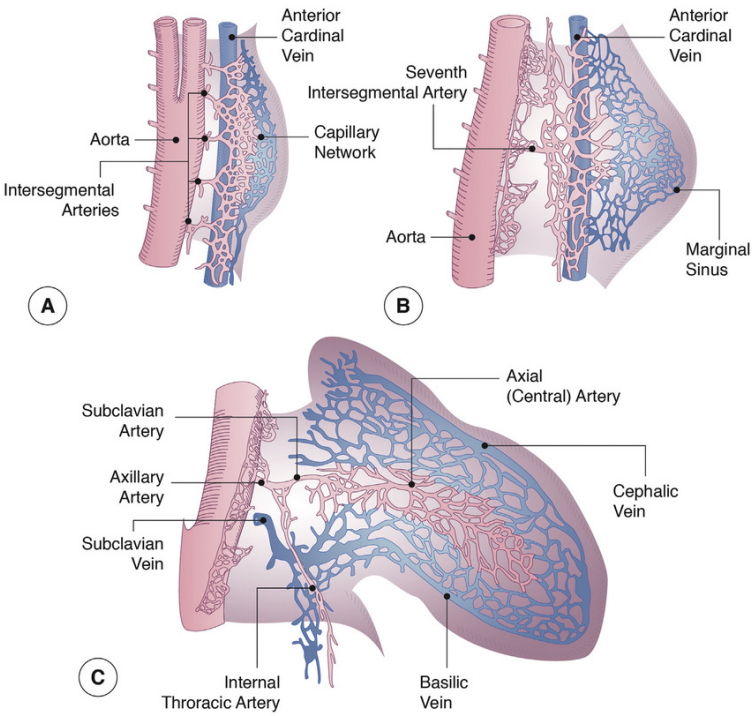
Limb Development
Limb Innervation

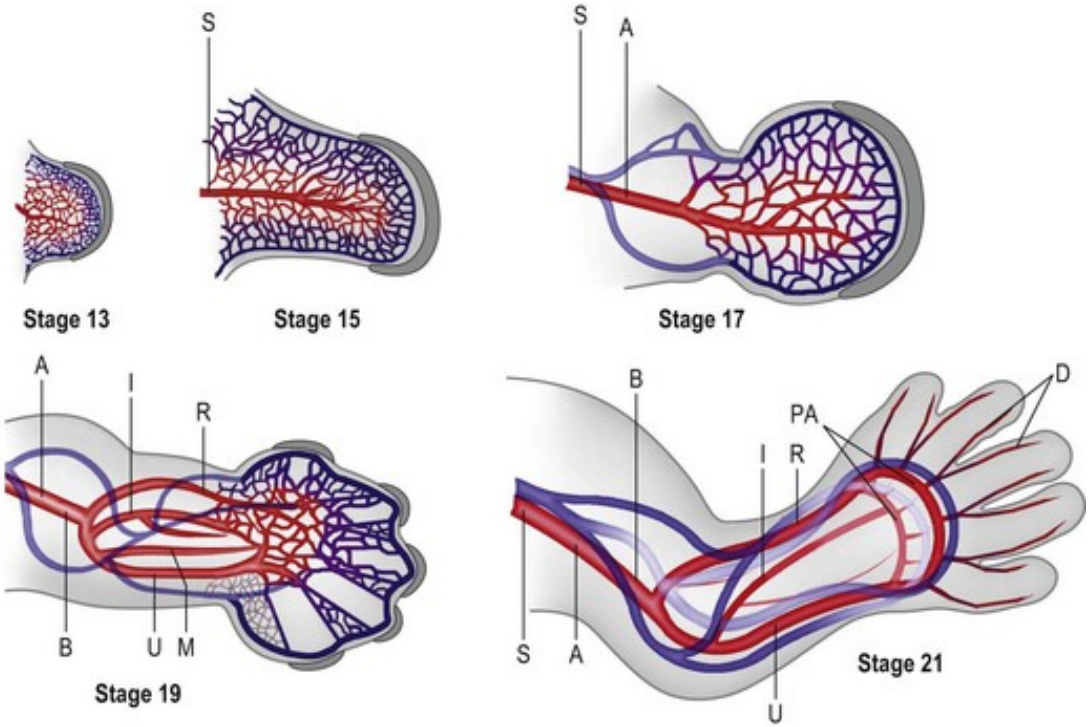


Hox6/10 code

Limb Development
Limb Vasculature

Angiogenesis from dorsal aorta
Vasculogenesis within Limb bud mesenchyme

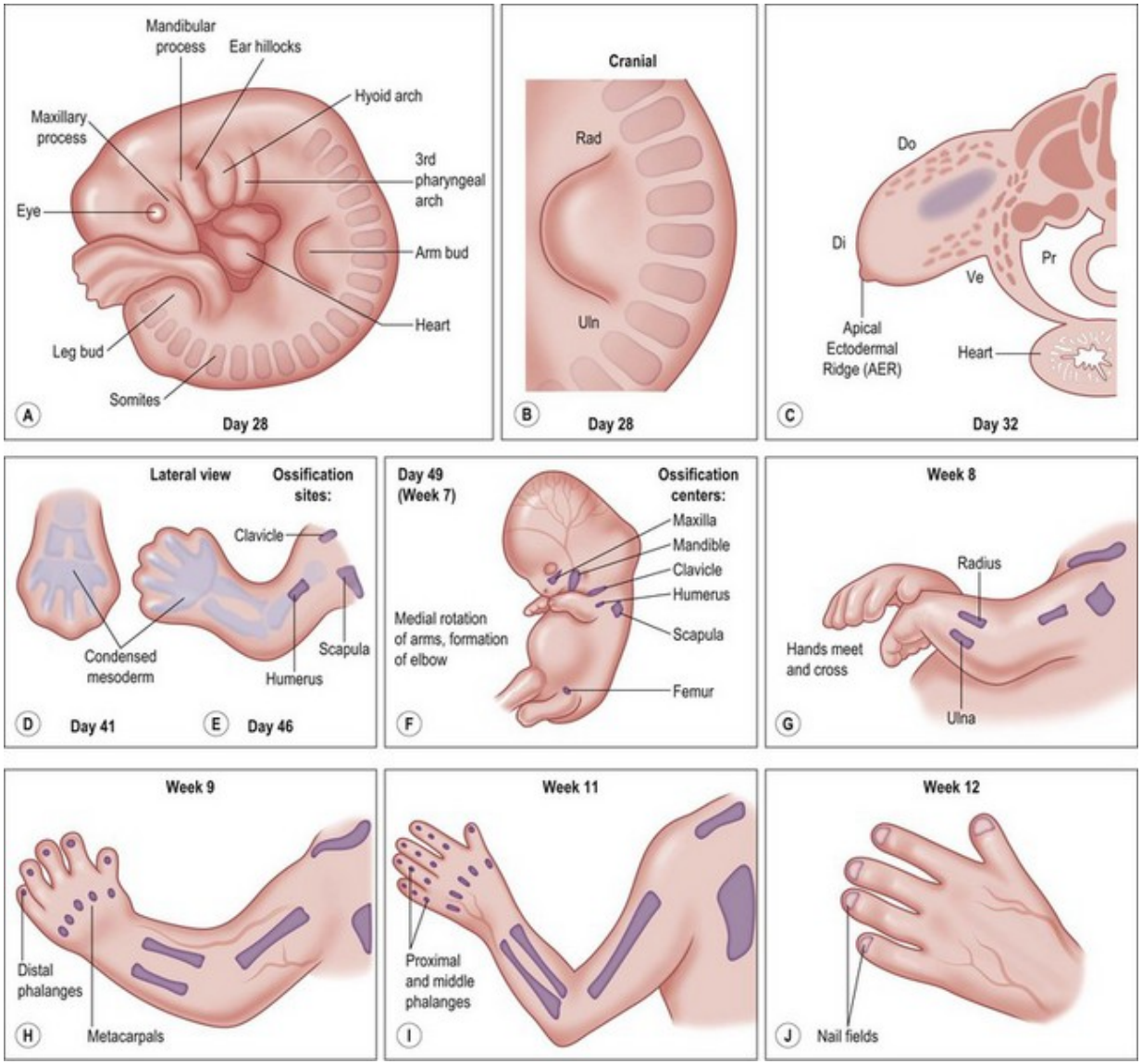




Limb Development
Limb rotation

8th week limbs rotate in different directions
thumb and toe rostral
knee and elbow face outward
upper limb rotates dorsally
lower limb rotates ventrally

Limb Development Summary



Lecture overview
Limb Development

Embryonic tissues contributing to limb development

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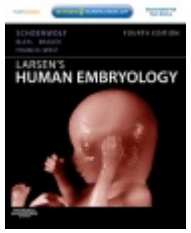
Autopod development

Limb skeleton, musculature, innervation, vasculature

Limb rotation

Relevant to Prac Class 8



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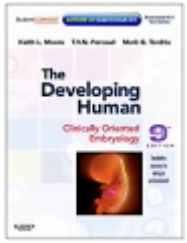

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