Limb Development

Resources:
http://php.med.unsw.edu.au/embryology/
Larsen’s Human Embryology
The Developing Human: Clinically Oriented Embryology

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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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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

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
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
Limb Development
Proximo-distal outgrowth

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

Cell Proliferation
Limb Development
Dorso-ventral patterning

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

Molecular control of dorsoventral (DV) patterning:

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

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

Active

β-catenin acts as transcriptional activator in the nucleus.

[Diagram showing WNT signalling pathway with β-catenin in the nucleus and at the membrane.]
Limb Development
Autopod development

Interdigital apoptosis
Limb Development
Autopod development
Limb Development
Limb Skeleton

Endochondral ossification

Stage 13
Stage 15
Stage 17
Stage 19
Stage 21

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Uln
Limb Development
Limb Musculature

Hypaxial myotome
Limb Development
Limb Musculature

Hypaxial myotome
Limb Development

Limb Innervation

Areas of sensation (dermatomes)

Cervical vertebrae (7) $C_1$-$C_7$

Thoracic vertebrae (12) $T_1$-$T_{12}$

Lumbar vertebrae (5) $L_1$-$L_5$

Sacrum (5 - fused)

Coccyx (4 - fused)
Limb Development
Limb Innervation

Stage 13
Stage 15
Stage 17
Stage 19
Stage 21

Hox6/10 code
**Limb Development**

**Limb Vasculature**

Angiogenesis from dorsal aorta
Vasculogenensis 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*
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Lecture overview
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Relevant to Prac Class 8

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