**The Cerebral Cortex: the frontal, dorsal and outer part of the brain**

Two Major Types of Neural Progenitor Cells：Polarized and non-polarized Neural Progenitor cells

**Progressive fate restriction**：Multipotent neural progenitor cells (NPCs) generates cortical projection neurons sequentially

**NPC heterogeneity**：Distinct types of neural progenitor cells (NPCs) for lower and upper layer neurons

**Lineage tracing** (fate mapping) is a method that delineates all progeny produced by a single cell or a group of cells. The possibility of performing lineage tracing initiated the field of Developmental Biology and continues to revolutionize Stem Cell Biology.

In a lineage-tracing experiment, the cells of interest are marked at one time point, and the progeny derived from these marked cells are revealed at a later time point.

(a) A careful assessment of the cells that are marked at the initial time point, so that the starting populations are clearly defined.

(b) The markers used to mark the cells remain exclusively in the original cells and their progeny and will not diffuse to the neighboring cells.

(c) These markers are sufficiently stable and are not toxic to the cells during the entire tracing period.

1. Direct observation：Direct observation is only suitable for studying simple   
   organisms that undergoes embryonic development   
   outside the mothers’ body.
2. Dye marking

Genetic labeling

1. Chimeric embryos (transplantation) Transgenic DNA chimeras
2. Cre-LoxP system（MADM）MosaicAnalysis withDoubleMarkers

**Gyrencephaly:** brains, such as that of humans, in which the cerebral cortex has convolutions

**Lissencephaly:** Lack of convolutional patterns in the cerebral cortex. Brains of rats and mice

1. Increase in the founder stem cell population
2. Increase rounds of transit amplification （为什么人脑大）
3. Longer period of neurogenesis

Development of the Gyrated Human Neocortex Involves a Lineage of Neural Stem and Transit-amplifying Cells that Forms the Outer Subventricular Zone

PDGFD–PDGFRb signaling is necessary for normal cell cycle progression of neocortical RG （radial glia）in humans

PDGFD–PDGFRb signaling is sufficient to promote RG identity in mice

**Key Facts in Cortical Development of Cerebrum**

Cortical projection neurons arise (directly or indirectly) from progenitor cells lying closed to the ventricle  
 New-born neurons migrate radially (outward) along the radial fibers of radial glial cells (RGCs)  
 Late-born neurons are laid on top of new-born neurons (insideout): I -VI -V -IV - III/II  
Gliogenesis follows neurogenesis  
 Precise neuronal migration ensures proper cortical layer formation  
 Interneurons are generated from the ventral part of the forebrain and migrate tangentially to the cortex

大脑皮层发育的关键事件

皮质放射性神经元（直接或间接）从靠近心室的祖细胞产生

新生的神经元沿径向胶质细胞（RGC）的放射状纤维径向（向外）迁移

晚出生的神经元被放置在新生的神经元之上（内部）

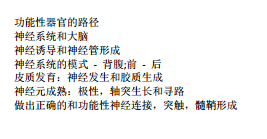
胶质细胞生成随神经发生

精确神经细胞迁移确保适当的皮质层形成

中间神经元由前脑的腹侧部分产生，并切向移动到皮层

**The Path to a functional Organ**

The nervous system and the brain  
Neural induction and neural tube formation  
Patterning of the nervous system- Dorsal-ventral; anterior-posterior  
Cortical development: neurogenesis and gliogenesis  
Neuronal maturation: polarity, axon growth and pathfinding  
Make the right and functional neural connections, synaptogenesis, myelination



QUIZ

1.Neural induction requires the inhibition of the epidermis inducing, anti-neural BMP4 signal. What’s the experimental proofs? X  
2. How is the ventral progenitor domains of spinal cord established? X

3.Please summarize key steps and mechanisms how patterning and regional subdividing of the neural tube are achieved

答：A-P patterning is under the regulation of several morphogens during development. The gradient of WNTs dictates the regionalization of the forebrain, mid-hindbrain, and anterior spinal cord, whereas gradients of RA and FGFs govern the spinal cord segmentation. D-V patterning in the forebrain (B) and spinal cord (C) is set by the dorsally derived morphogens WNTs and BMPs (yellow color) and the ventrally derived SHH (green color).

4.Characteristics of major types of neural progenitor cells in cortical development

Pax6: Radial glia cells

Tbr2: Basal progenitor cells

**Radial glial cells** are bipolar-shaped cells that span the width of the [cortex](https://en.wikipedia.org/wiki/Cerebral_cortex) in the developing vertebrate [central nervous system](https://en.wikipedia.org/wiki/Central_nervous_system) (CNS) and serve as primary [progenitor cells](https://en.wikipedia.org/wiki/Progenitor_cells) capable of generating [neurons](https://en.wikipedia.org/wiki/Neurons). During development, newborn neurons use radial glia as scaffolds, traveling along the radial glial fibers in order to reach their final destinations.

**Most neural progenies are derived from radial glial cells (RGCs).答RGC就行**

5.What is the experimental evidence showing the generation of layer-specific neurons is majorly cell-autonomous? PPT无  
6. What’re the underlying cellular mechanisms governing the expansion of human cortex?

1. Cortical projection neurons are born as an “inside-out”

fashion.

2. Cortical NPCs are largely progressive fate restrictive.

3. No sufficient proof for layer-specific cortical NPCs so far.

4. Progressive fate restriction and heterogeneity of

progenitor cells could be selectively used in different

developmental circumstances.

5. It’s elusive how progressive fate restriction is achieved.

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Gliogenesis follows neurogenesis  
 Precise neuronal migration ensures proper cortical layer formation  
 Interneurons are generated from the ventral part of the forebrain and migrate tangentially to the cortex

7.What is lineage tracing/fate mapping? What are common means to perform lineage tracing?见上

8.How to perform genetic lineage tracing? 见上

神经诱导需要抑制表皮诱导的抗神经 BMP4 信号。 什么是实验证明？

如何建立脊髓腹侧祖细胞结构域？

请总结如何实现神经管的图案化和区域细分的关键步骤和机制？

皮质发育中主要类型的神经祖细胞的特征？

什么是实验证据显示层特定神经元的产生主要是细胞自主的？

什么是控制人类皮层扩张的基本细胞机制？

什么是血统追踪/命运映射？ 什么是执行血统追踪的常见手段？

如何执行遗传谱系跟踪？

**Neural Crest Cells**

Derived from the ectoderm (neural fold) 源自外胚层

A transient structure 一个瞬态结构

Undergo an EMT and delamination from the dorsal neural tube

经EMT 和分离

Neural crest cells produce a variety of tissues (both mesoderm and ectoderm)

神经嵴细胞产生多种组织（中胚层和外胚层）

p.s. The epithelial–mesenchymal transition (EMT) is a process by which epithelial cells lose their cell polarity and cell-cell adhesion, and gain migratory and invasive properties to become mesenchymal (stem) cells; these are multipotent stromal cells that can differentiate into a variety of cell types. EMT is essential for numerous developmental processes including mesoderm formation and neural crest lineage. EMT has also been shown to occur in wound healing, in organ fibrosis and in the initiation of metastasis for cancer progression

上皮-间充质过渡(EMT)是上皮细胞失去细胞极性和细胞黏附的过程，并获得迁移和侵袭性的特性，成为间充质(干细胞)细胞;这些是可以分化成多种细胞类型的多效基质细胞。EMT是许多发育过程的关键，包括中胚层的形成和神经嵴的传承。EMT也出现在伤口愈合、器官纤维化和癌症转移的转移过程中。

**Specification of Neural Crest Cells:**

1. Neural crest cells first appear at the border between the presumptive epidermis and the presumptive neural plate.
2. The anterior border tissue become PLACODE基板, which generate eye, ear, nose, and other sensory organs.
3. The timing of BMP and Wnt expression is critical for discrimination between neural plate, epidermis, placode, and neural crest tissues.
4. Inductive mechanisms (FGF, BMP, Notch and Wnt signaling)–mesoderm, interaction between neural and non-neural ectoderm

神经嵴细胞的详述

1. 神经嵴细胞首先出现在假定表皮与推定神经板之间的边界处
2. 前缘组织变成基板，它产生眼睛，耳朵，鼻子和其他感觉器官
3. BMP和Wnt表达的时间对神经板，表皮，基板和神经嵴组织之间的区分至关重要。
4. 诱导机制（FGF, BMP, Notch和Wnt信号传导）—中胚层，神经和非神经外胚层之间的相互作用。
5. Pax7 as an early marker required for neural crest formation in avia embryos
6. The initiation of neural crest induction at or before gastrulation
7. Discrete regions of epiblast from stage 3–4 chick embryos are already specified to form neural crest
8. Medial epiblast is specified to form neural crest in the absence of definitive neural and early mesodermal markers
9. Establishment of a neural plate border might NOT be requisite for neural crest specification or induction, and that border formation and neural crest induction might be separable events
10. Pax7作为禽类胚胎中神经嵴形成所需的早期标记
11. 在原肠胚形成之前或形成时开始神经嵴 的诱导
12. 已经指定阶段3-4鸡胚的离散区域形成神经嵴
13. 指定内侧上胚层在没有明确的神经和早期中胚层标记的情况下形成神经嵴
14. 神经板边界的建立可能不是神经嵴规范或诱导的必要条件，并且边界形成和神经嵴诱导可能是可以分离的事件

**Sox10 Mediate Neural Crest Cell Differentiation:**

1. Delamination of neural crest cells from the neural tube.
2. Differentiation of the numerous neural crest lineages.
3. Sox10 binds to enhancers of target genes, which encode the neural crest effectors

**Sox10 介导神经嵴细胞分化**

1. 从神经管分离神经嵴细胞
2. 分化众多的神经嵴谱系
3. Sox10绑定到编码神经嵴效益器的目标基因的增强子

**通过用单个转录因子直接重编程产后成纤维细胞产生多能诱导的神经嵴**

1. Postnatal human fibroblasts can be reprogrammed into induced neural crest (iNC)

2. iNC can be generated by overexpression of SOX10 in combination with WNT activation

3. iNC cells exhibit capacity for multilineage differentiation and migration in vivo

4. Patient-derived iNC cells allow cellular modeling of neural crest diseases

1.产后人成纤维细胞可重编程为诱导神经嵴（iNC）

2.可以通过Sox10的过表达与Wnt活化结合产生Inc

3.Inc细胞表现出多向分化和体内迁移的能力

4.患者来源的Inc细胞允许神经嵴疾病的细胞建模

**Regionalization of the Neural Crest:**

1. Cranial NCCs: craniofacial mesenchyme, which differentiates into the cartilage, bone, cranial neurons, glia, pigment cells, and connective tissues of the face. These cells also enter the pharyngeal arches and pouches to give rise to thymic cells , the odontoblasts of the tooth primordia, and the bones of the middle ear and jaw.

2. Cardiac NCCs: a subregion of cranial NCC. Produce the entire muscular-connective tissue wall of the large arteries (the outflow tracts); the septum of the heart that separate pulmonary circulation from the aorta.

3. Trunk NCCs: 1) One group migrates ventrolaterally through the anterior half of each somatic sclerotome and form the dorsal root ganglia containing the sensory neurons. Cells that continue traveling more ventrally form the sympathetic ganglia, the adrenal medulla, and the nerve clusters surrounding the aorta. 2) Another group migrates dorsolaterally, allowing the precursors of melanocytes to move through the dermis from the dorsum to the belly.

4. Vagal and sacral NCCs generate the parasympathetic(enteric) ganglia

P.S Cranial crest cells can form cartilage, muscle, and bone, whereas trunk neural crest cells cannot. The inability of the trunk neural crest to form skeleton is most likely due to the expression of Hox genes in the trunk neural crest.

**神经嵴的区域化**

1. 头颅NCC：颅面间质，分化为软骨，骨，颅神经元，神经胶质细胞，色素细胞和结缔组织。这些细胞也进入咽弓和囊袋，产生胸腺细胞，牙原基的成牙质细胞以及中耳和下颌骨。
2. 心脏NCC:头颅NCC的一个子区域。产生大动脉的整个肌肉结缔组织壁（流出道）；将肺循环与主动脉分开的心脏隔膜
3. 躯干NCC：①一组通过每个体细胞核的前半部向腹外侧迁移，形成包含感觉神经元的背根神经节。继续行走的细胞腹部形成交感神经节，肾上腺髓质和围绕主动脉的神经丛。②另一组移行到背外侧，允许黑素细胞的前提以背部通过真皮移动到腹部。
4. 迷走神经和骶骨 NCC：产生副交感(肠)神经节

PS: 颅顶嵴细胞可以形成软骨，肌肉和骨骼，而躯干神经嵴细胞则不能。 躯干神经嵴形成骨架的能力很可能是由于躯干神经嵴中 Hox 基因的表达

**Mechanisms of Neural Crest Migration**

What signals initiate migration? (EMT – activation of the Wnt genes by BMPs)  
• When does the migratory agent (cells) become competent to respond to these signals? (when the somites cease making noggin)  
• How do the migratory agents know the route to travel? (attractant and repellent)  
• What signals indicate that the destination has been reached? (fully differentiated, MET)

神经嵴迁移的机制

•什么信号启动迁移？ （EMT-通过 BMP 激活 Wnt 基因）

•迁移中介（细胞）什么时候能够响应这些信号？ （当体节停止时）

•迁移中介如何知道迁移的路线？ （引诱剂和驱避剂）

•什么信号表明已达到目标？ （完全分化，MET）

Kit protein is essential for the proliferation and migration of neural crest cells, germ cell precursors, and blood cell precursors.

Kit 蛋白对神经嵴细胞，生殖细胞前体和血细胞前体的增殖和迁移至关重要。

**The Differentiation of the Trunk Neural Crest:**

1. Autonomous factors - Hox genes distinguishing trunk and cranial neural crest cells, MITF committing cells to a melanocytes lineage;

2. Specific conditions of the environment (vagal and thoracic neural crest);

3. A combination of two.

4. The fate of an individual neural crest cell is determined both by its starting position (A-P along the neural tube) and by its migratory path.

神经嵴的分化

1. 自主因素-Hox基因区分于躯干和颅神经嵴细胞，MITF将细胞分化为黑素细胞谱系；
2. 环境的具体情况（迷走神经和胸神经嵴）
3. 两个组合
4. 个体神经嵴细胞的命运由其起始位置（沿着神经管的A-P）和其迁移路径确定。

**Cranial Neural Crest:**

1. The head, comprising the face and the skull, is largely the product of the cranial neural crest.
2. Like the trunk neural crest, the cranial neural crest can form pigment cells, glial cells, and peripheral neurons.
3. It can generate bones, cartilage, and connective tissue.
4. In mice and humans, the cranial NCCs migrate from the neural folds even before they have fused together
5. Subsequent migration of NCCs is directed by an underlying segmentation of the hindbrain.
6. The cranial NCCs migrate ventrally into the pharyngeal arches and the frontonasal process(额鼻突)that forms the face
7. The final destination of cranial NCCs will determine their eventual fate.

**颅神经嵴**

1. 包括面部和头骨的头部很大程度上是颅神经嵴的产物
2. 就想躯干神经嵴一样，颅神经嵴可以形成色素细胞，神经胶质细胞和外周神经元。
3. 可以产生骨骼，软骨和结缔组织。
4. 在小鼠和人类中，颅神经嵴可以在融合在一起之前就从神经皱褶中迁移出来
5. 随后的NCC迁移由后脑的潜在分割（菱脑节）指导
6. 颅NCC从前侧迁移到咽弓和额鼻突形成脸部
7. 颅NCC的最终目的地将决定他们最终的命运

**Cranial Ectodermal Placodes (基板)**

1.Cranial ectodermal placodes are formed at the anterior borders between the   
epidermal and neural ectoderm.

2. Cranial placodes generate most peripheral sensory neurons of the head,   
associated with hearing, balance, taste, and smell.

1.颅外胚层基板形成于表皮和神经外胚层之间的前缘

2.颅基板产生头部的大部分外周感觉神经元，与听力，平衡，味觉和嗅觉有关

**Summary**

1.The neural crest is a transitory structure. Its cells migrate to become numerous different cell types.  
2.The formation of the neural crest depends on interactions between the prospective epidermis and the neural plate. Paracrine factors from these regions induce the formation of TFs that enable neural crest cells to emigrate.  
3.Some neural crest cells are capable of forming a large repertoire of cell types. Other neural crest cells may be restricted even before migration. The final destination of the neural crest cell can sometimes change its specification.  
4. The path a neural crest cell takes depends on the extracellular environment it meets.

5.Trunk neural crest cells can migrate dorsolaterally into the ectoderm, where they become melanocytes. They can also migrate ventrally, to become dorsal root ganglia cells, sympathetic and parasympathetic neurons and adrenomedullary cells.  
6. Trunk neural crest cells will migrate through the anterior portion of each sclerotome (骨节), but not through the posterior portion of a sclerotome. Semaphorin and ephrin proteins expressed in the posterior portion of each sclerotome can prevent neural crest cell migration.  
7.Cranial neural crest cells enter the pharyngeal arches to become cartilage of the jaw and the bones of the middle ear. They also form the bones of the frontonasal process, the papillae of the teeth, and the cranial nerves.

总结

1. 神经嵴是一个瞬时的结构。 它的细胞迁移成为许多不同的细胞类型。
2. 神经嵴的形成取决于前瞻性表皮和神经板之间的相互作用。 来自这些区域的旁分泌因子诱导使得神经嵴细胞迁移的转录因子的形成。
3. 一些神经嵴细胞能够形成大量的细胞类型。 其他神经嵴细胞甚至可能在迁徙之前受到限制。 神经嵴细胞的最终目标有时可以改变其规格。
4. 神经嵴细胞的路径取决于它遇到的细胞外环境。
5. 躯干神经嵴细胞可以背外侧迁移到外胚层，在那里他们成为黑素细胞。 它们 也可以迁移到腹侧，成为背根神经节细胞，交感神经和副交感神经元以及肾上 腺髓质细胞。
6. 躯干神经嵴细胞将通过每个骨节（骨节）的前部部分迁移，但不通过一个 骨节的后部。 信号素和在每个骨节的后部，能够防止神经嵴细胞迁移表达肝配 蛋白的蛋白质。
7. 颅神经嵴细胞进入咽弓成为下颌软骨和中耳骨。 它们也形成了额鼻骨的过程，牙齿的原基和颅神经。

QUIZ

• What are the main characteristics of neural crest cell lineages?

A transient structure 一个瞬态结构

Undergo an EMT and delamination from the dorsal neural tube

经EMT 和分离

Neural crest cells produce a variety of tissues (both mesoderm and ectoderm)

神经嵴细胞产生多种组织（中胚层和外胚层）

• Where are neural crest cells derived?

Derived from the ectoderm (neural fold) 源自外胚层

• Why the neural crest cell lineages are called as “the fourth germ layer”? Please give a few examples which cell types neural crest cells can generate.

1. Cranial NCCs: craniofacial mesenchyme, which differentiates into the cartilage, bone, cranial neurons, glia, pigment cells, and connective tissues of the face. These cells also enter the pharyngeal arches and pouches to give rise to thymic cells , the odontoblasts of the tooth primordia, and the bones of the middle ear and jaw.

2. Cardiac NCCs: a subregion of cranial NCC. Produce the entire muscular-connective tissue wall of the large arteries (the outflow tracts); the septum of the heart that separate pulmonary circulation from the aorta.

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4. Vagal and sacral NCCs generate the parasympathetic(enteric) ganglia

• What’s the main differences between trunk and cranial neural crest cells? And what’s the underlying molecular mechanism?

起点的位置不一样，产生的组织不一样，迁移的方式

Autonomous factors - Hox genes distinguishing trunk and cranial neural crest cells, MITF committing cells to a melanocytes lineage;

• Trunk neural crest cells will migrate through the anterior portion of each sclerotome, but not through the posterior portion of a sclerotome. What’s the   
underlying molecular mechanism?

Trunk neural crest cells will migrate through the anterior portion of each sclerotome (骨节), but not through the posterior portion of a sclerotome. Semaphorin and ephrin proteins expressed in the posterior portion of each sclerotome can prevent neural crest cell migration.

• What are mechanisms of neural crest migration?

What signals initiate migration? (EMT – activation of the Wnt genes by BMPs)  
• When does the migratory agent (cells) become competent to respond to these signals? (when the somites cease making noggin)  
• How do the migratory agents know the route to travel? (attractant and repellent)  
• What signals indicate that the destination has been reached? (fully differentiated, MET)

• What are mechanisms of neural crest differentiation?

Pax7 Hox10

1. Autonomous factors - Hox genes distinguishing trunk and cranial neural crest cells, MITF committing cells to a melanocytes lineage;

2. Specific conditions of the environment (vagal and thoracic neural crest);

3. A combination of two.

4. The fate of an individual neural crest cell is determined both by its starting position (A-P along the neural tube) and by its migratory path.

**Stem cell biology**

定义：**Stem cells: A relatively undifferentiated cell that when it divides produces (1) at least one of two daughter cells that retains its undifferentiated character (self-renewal); and (2) a daughter cell that can undergo further differentiation.**

**干细胞：一种相对未分化的细胞，当其分裂时产生**

* 1. **保留其未分化特征的至少一个子细胞（自我更新）**
  2. **可以进一步分化的子细胞**

**Pluripotent stem cells: Cells able to make an animal**

1. Totipotent cells (zygote and the blastomeres) –Capable of forming every cells in the embryo and the trophoblast cells of the placenta
2. Pluripotent stem cells (inner cell mass and undifferentiated germ cells) -Capable of forming every cells in the embryo but NOT the trophoblast cells of the placenta

Pluripotent stem cells are self-renewing cells with the capacity to form representative tissues of all three germ layers（胚层）of the developing embryo - ectoderm, mesoderm and endoderm, as well as the germ lineage, but typically provide little or no contribution to the trophoblast layers of placenta. Pluripotent stem cells can be derived from numerous sources.

1.全能细胞（合子和卵裂球）——能够形成胚胎的每个 细胞和胎盘的滋养层细胞 2.多能干细胞（内细胞团和未分化的生殖细胞）——能够 在胚胎中形成每个细胞，但不能形成胎盘的滋养层细胞。多能干细胞是自我更新的细胞，具有形成发育中的胚胎所有三个胚 层——外胚层、中胚层和内胚层、以及生殖系的代表性组织的能力，但 是通常对滋养层胎盘几乎没有贡献。多能干细胞可以来自许多来源。

**Embryonic stem cells (ESCs)** are pluripotent stem cells derived from the Inner cell mass of a blastocyst囊胚, an early-stage preimplantation embryo.

**胚胎干细胞**是来源于囊胚的内细胞团的多能干细胞

**Characteristics of pluripotent stem cells：**

**Molecular properties：分子性质**

1. Expression of stem cell markers: OCT4, NANOG, SOX2, etc.

2. Epigenetic status: loosed chromatins; DNA hypomethylation; X chromosome activation.

1.干细胞标志物的表达：OCT4, NANOG, SOX2等.

2.表观遗传状态：染色体松散，DNA甲基化，X染色体活化。

**Phenotypic properties：表型特征**

1. In vitro differentiation; produce progenies that belong to all three germ layers [form embryonic bodies (拟胚体) in vitro];

2. Teratoma (畸胎瘤) formation in vivo; embryo chimaras;

3. Reconstitute a fetus (gestational complementation, germline transmission, tetraploid complementation, and single-cell chimeras).

1.体外分化：产生属于所有三个胚层的后代（在体外形成拟胚体）

2.畸胎瘤体内形成：胚胎嵌合体

3.胎儿的再构成（妊娠互补，种系传递，四倍体互补和单细胞嵌合体）

**Assays employed to reveal the developmental potential of pluripotent stem cells:**

(1) In vitro differentiation;

(2) Teratoma formation;

(3) Chimera formation;

(4) Germline transmission;

(5) Tetraploid complementation;

(6) single-cell chimaera formation

用于揭示多能干细胞发育潜力的分析：

(1) 体外分化 ;

(2) 肿瘤形成 ;

(3) 嵌合体形成 ;

(4) 种系传播 ;

(5) 四倍体互补 ; （四倍体的细胞能增加胚外组织,但不是胎儿本身。）

(6) 单细胞嵌合体形成

**Adult stem cells: Cells able to replenish a tissue**

1. **Multipotent (hematopoietic stem cells)** multipotent stem cells can be in either the embryo or the adult, and their commitment is limited to a

relatively small subset of all the possible cells of the body

1. **Unipotent (Spermatogonia, 精原细胞)** only involved in regenerating a particular type of cell
2. **Progenitor cells (Basal neural progenitors)** limited self-renew capabilities. They have the capacity to divide only a few times before differentiating.

成体干细胞：能够补充组织的细胞

1. 多功能（造血干细胞）：多功能干细胞可以在胚胎或成人中，它们的作用仅限于身体所有可能细胞的相对较小的分子集。
2. 专能（精原细胞）：仅涉及再生一种特定类型的细胞
3. 祖细胞（基底神经祖细胞）：有限的自我更新能力，在分化之前，它们只能分割几次。

**How to derive pluripotent stem cells?**

• ES cells: cells derived from Inner Cell Mass – “ICM”; cells develop into the fetus

• Somatic cell nuclear transfer (SCNT, cloning)

• Cell fusion

• Reprogrammed - induced pluripotent stem cells (iPSCs)

**如何衍生多能干细胞？**

•ES 细胞：源自内细胞团的细胞 - “ICM”; 细胞发育成胎儿

•体细胞核移植（SCNT，克隆）

细胞融合

•重编程诱导多能干细胞（iPSCs）

**Stem cell niches** are particular locations (environment) that allow the controlled self-renewal and survival of the stem cells within the niche and the Controlled differentiation of those stem cell progeny that leave the niche

**干细胞生态位**是特定的位置（环境），其允许干细胞在生态位内的受控自我更新和存活以及那些离开生态位的干细胞子代的受控分化

**Stem Cell Niche in Drosophila Testes**

Hub cells secrete Unpaired to activate the JAK-STAT pathway in the   
adjacent germ stem cells to specify their self-renewal

**干细胞在果蝇睾丸生态位**

Hub 细胞分泌不配对以激活相邻生殖干细胞中的 JAK-STAT 途径以指定其自我更新。

**The Hematopoietic Stem Cell Niche**

The HSC niches is in the endosteum (the bone marrow close to the bone)  
 In the niche, the HSCs are in close proximity to bone cells and the endothelial cells and pericytes that line the blood vessels.   
 Paracrine factors and cell-surface signals

造血干细胞生态位

HSC 生态位位于骨内膜（接近骨的骨髓）

在小生境中，HSC 靠近骨细胞和沿血管排列的内皮细胞和周细胞。

旁分泌因子和细胞表面信号

**Lgr5–A true stem cell marker for small intestine and colon**

1. A Wnt target gene -leucine-rich-repeat containing G protein-coupled receptor 5
2. Down-regulated on the induced inhibition of Wnt pathway in CRC cell lines
3. Expressed in the crypts, but not in the villi
4. Lgr5-positive cells locate at all crypt bottoms, distinct from Paneth cells or TA cells
5. Lgr5-positive cells generate all epithelial lineages in the small intestine and colon

6. The expression pattern of Lgr5 suggests that it marks stem   
cells in multiple adult tissues and cancers

**Lgr5 - 小肠和结肠真正的干细胞标志物**

1. Wnt 靶基因 - 富含亮氨酸的重复序列含 G 蛋白偶联受体 5
2. 在 CRC 细胞系中诱导 Wnt 通路的抑制下调
3. 在隐窝中表达，但不在绒毛中
4. Lgr5 阳性细胞位于所有隐窝底部，与 Paneth 细胞或 TA 细胞不同
5. Lgr5 阳性细胞在小肠和结肠中产生所有的上皮细胞系
6. Lgr5 的表达模式表明其标记在多种成体组织和癌症中的干细胞

**A comparison between iPSc derived progenies and trans-differentiation！！！**

|  |  |  |
| --- | --- | --- |
|  | **Differentiation from ES/iPS** | **trans-differentiation** |
| Pros | **1) Known factors for iPS reprogramming**  **2) Can be virus free**  **3) Cultured in vitro–controllable**  **4) Can generate large amount of cells**  **5) May produce all cell types** | **1) single step**  **2) Can be achieved in vivo**  **3) Less prone to mutation**  **4) Can be virus free** |
| Cons | **1) Multiple steps**  **2) Mutation culmination –cancer** | **1)Specific combinations for each cell type**  **2) Low efficiency, very limited numbers of cells** |

**iPSc 衍生后代与转分化的比较**

|  |  |  |
| --- | --- | --- |
|  | **与 ES / iPS 差异化** | **反转分化** |
| 优点 | 1）iPS 重编程的已知因素  2）可以在体内实现  3）不易发生突变  4）可以是无病毒的细胞  5）可以产生所有细胞类型 | 1）单步  2）可以无病毒  3）体外培养 - 可控  4）可以产生大量的 |
| **缺点** | 1）多个步骤  2）突变高潮 - 每种细胞类型的癌症（未知） | 1）特定的组合  2）效率低，细胞数量非常有限 |

**Quiz  
• What are pluripotent and adult stem cells?**

**Pluripotent stem cells: Cells able to make an animal）（ES）**

**Adult stem cells: Cells able to replenish a tissue（造血，精原，祖细胞）**

**• What are the similarities and differences between totipency (全能),   
pluripotency (多能) and multipotency? 分别对应胚胎发育中的哪些阶段？**

1.Totipotent cells (zygote and the blastomeres) –Capable of forming every cells in the embryo and the trophoblast cells of the placenta .

2.Pluripotent stem cells (inner cell mass and undifferentiated germ cells) -Capable of forming every cells in the embryo but NOT the trophoblast cells of the placenta. Pluripotent stem cells are self-renewing cells with the capacity to form representative tissues of all three germ layers（胚层）of the developing embryo - ectoderm, mesoderm and endoderm, as well as the germ lineage, but typically provide little or no contribution to the trophoblast layers of placenta. Pluripotent stem cells can be derived from numerous sources.

Multipotency, 成体干细胞（造血等）

**• How to experimentally characterize pluripotent stem cells? Checklist, gold   
standard?**

(1) In vitro differentiation;

(2) Teratoma formation;

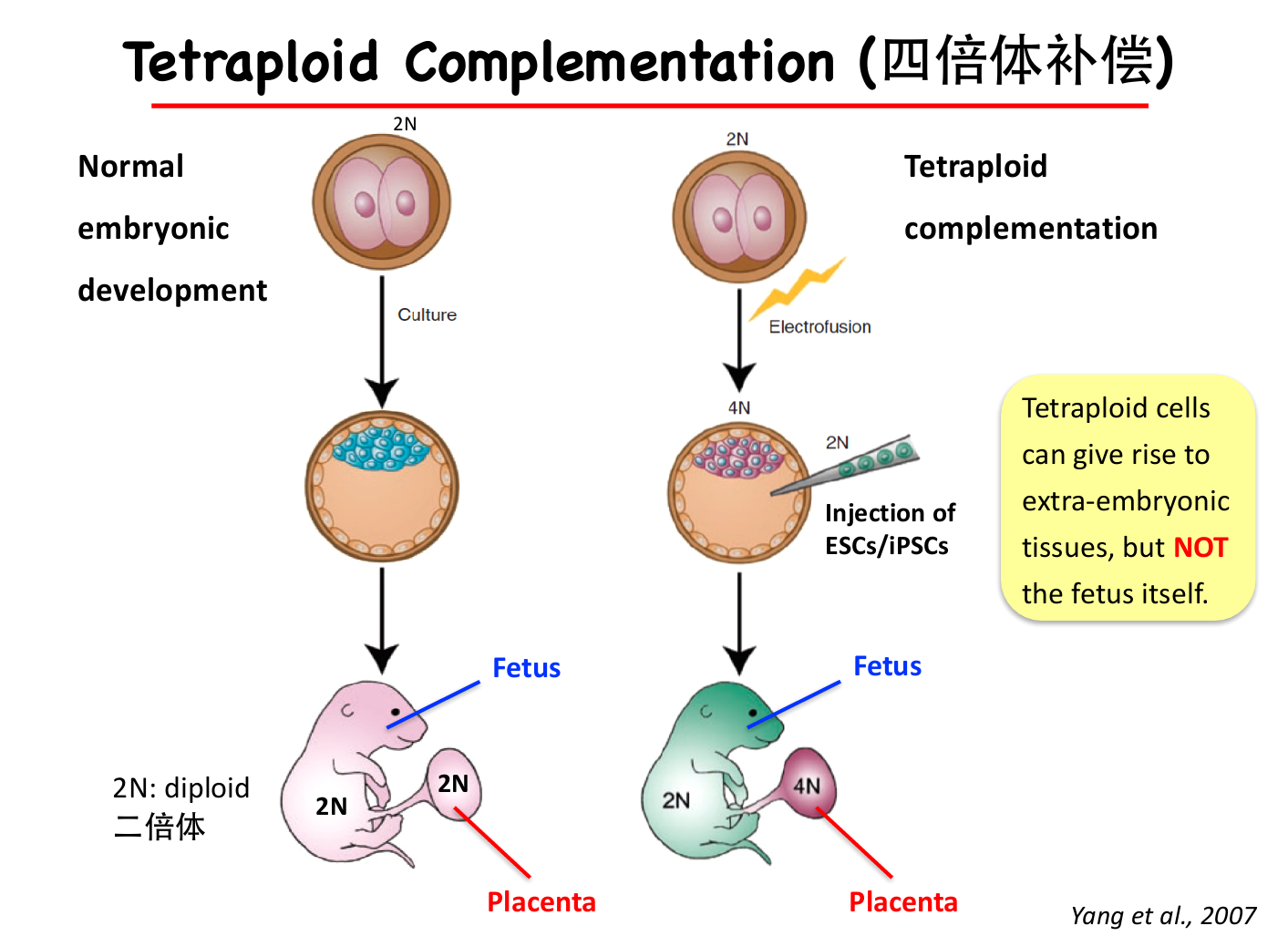
(3) Chimera formation;

(4) Germline transmission;

(5) Tetraploid complementation;

(6) single-cell chimaera formation

**能发育成完整个体的，pluripotent  
• Please describe the experiments of tetraploid complementation**

 **• What can embryonic stem cells and iPSCs do?**

**• Study human development**

**in culture dishes；**

**• Disease modeling；**

**• Drug screening;**

**• Produce functioning terminal cells to replenish damaged/lost cells and**

**tissue.  
• What’re the advantages of iPSCs?**

**• Ethical issues:**

**- Destroying human embryos for ES cells**

**- Somatic nuclear transfer – requiring unfertilized eggs/oocytes**

**• Host-vs-graft rejection issues  
• What are the stem cell niches?见上  
• How to experimentally characterize adult stem cells?**

**介绍那个肠道的干细胞，实验证明他可以分裂分化成多种细胞，更新组织  
• Please compare the advantage and disadvantages using progenies from   
iPSCs or trans-differentiation见上**

**Somatogenesis**

**Regeneration：**

|  |  |  |
| --- | --- | --- |
|  | Process | Examples |
| Stem-cell mediated regeneration | Stem-cell mediated regeneration | Planarian/flatworm, skin, hair, blood |
| Epimorphosis  新建再生、割处再生、 表变态 | dedifferentiation, re differentiation | Amphibian limb |
| Morphallax 变形再生、形态重组 | Re-patterning of existing tissues, little new growth | Hydra |
| Compensatory regeneration | Differentiated cells divide | Mammalian liver |
|  | Process | Examples |
| 干细胞引起的再生 | 干细胞引起的再生 | 扁 虫 / 扁 虫，皮肤， 头发，血液 |
| Epimorphosis  新建再生、割处再生、 表变态 | 去分化、再分化 | 两栖动物 肢体 |
| Morphallax 变形再生、形态重组 | 现有的组织重新构图，新的增长很少 | 水螅 |
| 补偿性再生 | 分化的细胞分裂 | 哺乳动物 肝脏 |

Salamanders accomplish epimorphic regeneration by cell dedifferentiation to

Form a regeneration blastemal -an aggregation of relatively undifferentiated cells derived from the originally differentiated tissue-which then proliferates and redifferentiates into the new limb parts

**蝾 螈 四 肢 的 外 形 再生**

蝾螈通过细胞去分化完成表型再生，形成再生的 blastma（原基） -一种来源于最初分化组织的相对未分化细胞的聚集 - 然后增殖并再分化为新的肢体部位

**Major Lineage of the Amniote Mesoderm：**

1. Chordamesoderm(脊索中胚层) forms the notochord

2. Paraxial/somitic(轴旁/体节) mesoderm forms the somites and head mesoderm –Somites are blocks of mesodermal cells on either side of the neural tube, which produce muscle and many of the connective tissues of the back (dermis, muscle, vertebrae and ribs) –Head mesoderm(anterior), along with the cranial neural crest, forms the skeleton, muscles, and connective tissue of the face and skull Major Lineage of the Amniote Mesoderm

3. Intermediate mesoderm forms the urogenital system, including the kidneys, the gonads, and their associated ducts. And the outer (cortical) portion of the adrenal gland.

4. Lateral plate mesoderm

Splanchnic (脏壁) mesoderm: heart, blood vessels, blood cells

Somatic mesoderm (体壁): lining of the body cavities; pelvic and limb skeleton.

Extraembryonic(胚外) mesoderm

**主要的脊椎动物中胚层谱系**

1.脊索中胚层（Chordamesoderm）形成脊索

2.旁轴/体节中胚层形成体节和头中胚层

体节是神经管两侧的中胚层细胞块，它产生肌肉和背部的许多结缔组织（真皮，肌肉，椎骨 和肋骨）

- 头部中胚层（前）与颅神经嵴一起形成面部和头骨的骨骼，肌肉和结缔组织

3.中胚层形成泌尿生殖系统，包括肾脏，生殖腺及其相关导管。 和肾上腺的皮层（皮质）部 分。

4.侧板中胚层

- 脏壁中胚层：心脏，血管，血细胞

- 体壁（Somatic mesoderm）：体腔的内衬; 骨盆和四肢骨架。

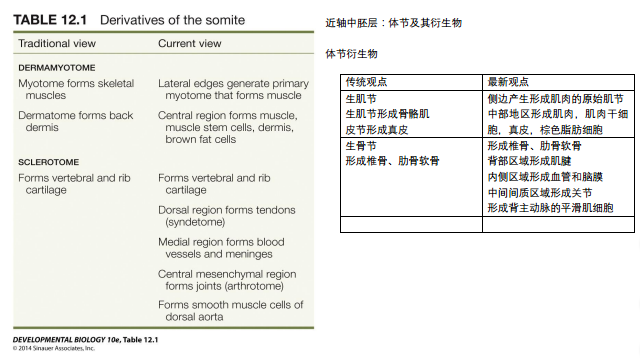
- 胚外（胚外）中胚层

**The Paraxial Mesoderm is Specified by the Antogonism of BMP Signaling**

Noggin is synthesized by the early presomitic mesoderm. If Noggin-expressing cells are placed into presumptive lateral plate mesoderm, the lateral plate tissue will be re-specified into somite-forming paraxial mesoderm.

**近轴中胚层是由 BMP 信号的抑制作用指定的**

Noggin 是由早期的中胚层中胚层合成的。 如果 Noggin 表达细胞被置于假定的侧板中胚层中，则外 侧板组织将被重新指定到形成体节的近轴中胚层。



**Formation of the Somites -Somitogenesis**

1. Presomitic mesoderm (PSM前体节中胚层)

2. Periodicity: clock and wavefront

3. Synchronicity

4. Fissure formation (separation of the somites)

5. Epithelialization

6. Specification

7. Differentiation

体节的形成——体节发生

1.前体节中胚层（PSM，前体节中胚层）

2.周期性：“时钟和波前”

3.同步

4.裂隙形成（体节分离）

5.上皮化

6.规格

7.分化

The wave of expression is not due to cell movement but to individual cells turning on and off gene expression in asynchronized （同步化）and periodic （周期性）fashion. This is an intrinsic property of the PSM tissue.

Once the wave reaches the anterior limit of the PSM, a somite pair buds off and a new wave of expression is initiated in the posterior PSM

**What are the segmentation clock pacemaker：**

1. The periodic expression of the Notch ligands could trigger the molecular oscillations of Notch signaling
2. At least in the case of the Notch pathway, the generation and maintenance of oscillations along the PSM have been shown to rely on negative feedback loops driven by clock genes (unstable negative regulators) of the pathway that are encoded by the clock genes.
3. Hes7 protein constitutively represses Hes7 and Lfng gene transcription

**Molecule basis of Synchronicity**

1. Her-MO cells are expected to continuously activate Notch signaling in surrounding cells, because the expression of deltaC is upregulated due to the absence of Her1/7 dependent repression
2. This segment shift activity of Her-MO cells was also found to depend upon the function of DeltaC, as its depletion in donor cells abolishes the segment-shift activity of Her-MO cells

**Translating the Periodic Signal into Repeated Segments:**

1. The Mesp2 stripe forms in the anterior PSM in response to the periodic clock signal at a level defined as the determination front, and it defines the future somatic boundaries.
2. Antagonistic gradients of FGF/Wnt signaling and retinoic acid signaling position the determination front.
3. Cells that reach the determination front are exposed to the periodic clock signal, initiating the segmentation program and activating simultaneously expression of genes such as Mesp2 in a stripe domain that prefigures the future segment.

**Muscle Development:**

1. Myogenic regulatory factors (MRF) are bHLH TFs, including MyoD, Myf5, myogenin and Mrf4.
2. Each member of this family can activate the genes of the other family members, leading to positive feedback regulation so powerful that the activation of an MRF in nearly cells in the body converts that cell into muscle.

**• Satellite Cells**

Populations of stem cells and progenitor cells that reside alongside the adult muscle fibers, which are responsible for the growth and regeneration of muscles.

**QUIZ  
• What are major derivatives of the mesoderm?  
• What are the molecular basis for periodic clocks in somitogenesis?  
• The molecular basis for synchronicity inside a somite  
• How to translate the periodic signal into repeated segments of somites?  
• Please summarize the process of muscle development  
• What are the key features of myogenic transcription factors?**

** 中胚层的主要衍生物是什么？ ·**

** 周期性时钟在体节发生中的分子基础是什么？ ·**

** 体节同步性的分子基础**

** 如何将周期性信号转化为躯体的重复分节？ ·**

** 请概述肌肉发育的过程**

** 肌原性转录因子的主要特征是什么？**

**Limb development**

**How to Identify the Limb Field?**1. Removing certain groups of cells and observing that a limb does not develop in their absence. (Detwiler1918; Harrison 1918)  
2. Transplanting groups of cells to a new location and observing that they form a limb in this new place. (Hertwig 1925)  
3. Marking groups of cells with dyes or radioactive precursors and observing that their descendants participate in limb development. (lineage-tracing)

如何识别肢体领域？

1.去除某些细胞群，然后发现肢体缺少他们后不发育。 （Detwiler 1918; Harrison 1918）

2.将细胞群移植到一个新的位置，并观察它们在这个新的地方形成一个肢体。 （Hertwig 1925）

3.标示用染料或放射性前体细胞群，并观察他们的子代细胞参与肢体发育。（谱系 追踪）

Emergence of the Limb Bud

• Limb development begins when mesenchyme cells migrate from the limb fields of the lateral plate mesoderm (to form the limb skeletal precursor cells ) and from the somites (the limb muscle precursor cells) at the same level.  
• These mesenchymal cells accumulate under the skin(ectodermal) tissue to create a   
circular bulge called a limb bud.  
• Vertebrates have no more than four limb buds per embryo, and limb buds are always paired opposite each other with respect to the midline

肢芽的浮现

•当间质细胞从肢体区域的侧板中胚层迁移（形成肢体骨骼前体细胞）和从体节迁移的（肢体肌肉前体细胞）处于同一水平 时，肢体开始发育。

•这些间充质细胞在皮肤（外胚层）组织下聚集形成一个称为 肢芽的圆形凸起。 •每个胚胎的脊椎动物的四肢芽不超过四根，而且肢芽相对于 中线总是成对的对立的。

**Induction of the early limb buds: Wnt proteins and fibroblast growth factors (Fgfs)**

1.Hox proteins establish conditions for the synthesis of retinoic acid in the lateral plate   
mesoderm.  
2. RA causes the induction of transcription factors Tbx5 (forelimb) and Tbx4 (hindlimb).  
3. The Tbx TFs induce Fgf10 in the lateral plate mesoderm.  
4. Fgf10 induces Fgf8 expression in the ectoderm via Wnt signaling.  
5. The positive feedback loop between Fgf10 in the mesoderm and Fgf8 in the ectoderm   
initiates the outgrowth of the limb and forms the apical ectodermal ridge (AER).

**诱导早期肢芽：Wnt 蛋白质和成纤维细胞生长因子（Fgfs）**

1.Hox 蛋白为侧板中胚层合成维甲酸创造了条件。

2.RA 引起转录因子 Tbx5（前肢）和 Tbx4（后肢）的诱导。

3. Tbx TFs 在侧板中胚层诱导 Fgf10。

4. Fgf10 通过 Wnt 信号在外胚层诱导 Fgf8 表达。

5.中胚层中的 Fgf10 与外胚层中的 Fgf8 之间的正反馈循环引发了肢体的生长并形成了顶部外胚层脊（AER）。

**前肢或后肢的特化通过 Tbx5 和 Tbx4**

**The apical ectodermal ridge (AER)**  
When mesenchyme cells enter the limb field, they secrete Fgf10 that induces the overlying ectoderm to form the apical ectodermal ridge (AER). The AER runs along the distal margin of the limb bud and will become a major signaling center for the developing limb

**顶端外胚层（AER）**

当间充质细胞进入肢体区域时，它们分泌 Fgf10，诱导上覆的外胚层形成顶部 外胚层脊（AER）。 AER 沿着肢芽的远端边缘运行，并将成为发育肢体的主要信号中心。

1.If the AER is removed at any time during limb development, further development of distal limb skeletal elements ceases.  
2. If an extra AER is grafted onto an existing limb bud, supernumerary  
structures are formed, usually toward the distal end of the limb.  
3. If leg mesenchyme is placed directly beneath the wing AER, distal   
hindlimb structures (toes) develop at the end of the limb. However,   
if this mesenchyme is placed farther from the AER, the hindlimb  
(leg) mesenchyme becomes integrated into wing structures.  
4. If limb mesenchyme is replaced by nonlimb mesenchyme beneath   
the AER, the AER regresses and limb development ceases.   
5. Fgfs are critical for the induction, maintenance, and function of the   
AER.

1.如果在肢体发育期间随时切除 AER，则远端肢体骨骼元素的进一步发展停止。

2.如果额外的 AER 被嫁接到现有的肢芽上，则形成多余的结构，通常是朝向肢体的远端。

3.如果腿间质被直接放置在翼 AER 的下面，则在肢体末端形成远侧后肢结构（脚趾）。 然而，如果这个间质离 AER 更远，后肢（腿）间质就会整合到翼结构中。

4.如果肢体间质由 AER 下面的非肢体间质代替，则 AER 消退，肢体发育停止。

5. Fgfs 对 AER 的诱导，维持和功能至关重要。

**Control of Proximal-distal Specification by the Distal (Progress Zone) Mesenchyme**

An extra set of ulna and radius formed when an early wing-bud progress zone was transplanted to a late wing bud that had already formed ulna and radius.  
Lack of intermediate structures seen when a late wing-budprogress zone was transplanted to an early wing bud.

**远端（渐进区）间质控制近端 - 远端的特化**

当一个早期的翅芽渐进区被移植到一个已经形成尺骨和桡骨的晚翼芽时，一个额外的尺骨和桡骨会形成。

当一个晚期的翅芽渐进区被移植到一个早期的翅芽时，会缺乏中后期结构。

**肢体模式的双梯度模型**

RA从移植的间质近端化骨骼的形成；

FGFs 和 Wnts 从移植的间质远端化骨骼的形成

**The zone of polarizing activity (ZPA)极性活化区**

• ZPA is a small block of mesodermal tissue near the posterior junction of the young limb bud and the body.  
• When a ZPA is grafted to anterior limb bud mesoderm, duplicated digits emerge as a mirror image of the normal digits.

•ZPA 是靠近年轻肢芽和身体后部交界处的一小块中胚层组织。

•当 ZPA 移植到前肢中胚层时，重复的手指成为正常手指的镜像。

**Sonic hedgehog defines the ZPA, therefore Specifies the Anterior-posterior Axis**

**Shh界定 ZPA，因此特化前后轴极性**

**Regulation of Digit Identity by BMP Concentration in the Interdigital Mesoderm Posterior to the Digit**

**手指后面交叉指型的中胚层 BMP 浓度调控手指特征**

**Regulation of digit identity by BMP concentrations in the interdigital space anterior to the digit and by Gli3**

**通过在手指前面的指间空间中的 BMP 浓度和通过 Gli3 调节手指特征**

**Wnt7a Specifies the Dorsal-Ventral Axis**

**Wnt7a 特化背腹轴极性**

**The BMP Signal Eliminates Growth and Patterning along all Axis**• Wnt7a-dificient mice lacked both dorsal limb structure and posterior digits. (loss of Shh)  
• At the end of limb patterning, BMPs are responsible for simultaneously shutting down the AER, indirectly shutting down the ZPA, and inhibiting the Wnt7a signal along the dorsal-ventral axis.

BMP 信号消除沿所有轴的生长和模式化

•缺乏 Wnt7a 的小鼠缺乏背肢结构和后指。 （失去 Shh）

•在肢体模式结束时，BMP 负责同时关闭 AER，间接关闭 ZPA并抑制沿背腹轴的 Wnt7a 信号。

**Summary**1. The positions where limbs emerge from the body axis depend on Hox  
gene expression  
2. The positive feedback loop between Fgf10 in the mesoderm and Fgf8 in   
the ectoderm initiates the outgrowth of the limb and forms the apical   
ectodermal ridge (AER).  
3. Two opposing gradients, one of Fgfs and Wnts from the AER, the other   
of retinoic acid from the flank, pattern the limb.  
4. The anterior-posterior axis is defined by the expression of Sonic   
hedgehog in the zone of polarizing activity (ZPA), a region in the   
posterior mesoderm of the limb bud.   
5. Shh specifies digits in at least two ways. It works through BMP inhibition   
in the interdigital mesenchyme, and it also regulates the proliferation of   
digit cartilage.  
6. Mutations in the long-range enhancer for Shh can cause polydactyly by   
creating a second ZPA in the anterior margin of the limb bud.  
7. The dorsal-ventral axis is formed in part by the expression of Wnt7a in   
the dorsal portion of the limb ectoderm.

**总结**

1. 肢体从身体轴线出现的位置取决于 Hox 基因的表达

2. 中胚层中的 Fgf10 与外胚层中的 Fgf8 之间的正反馈循环引发肢体的生长并形成顶端外胚层脊（AER）。

3. 两个相反的梯度，一个来自 Fgfs 和 AER 的 Wnts，另一个来自腹侧的RA（retinoic acid），决定肢体。

4. 前 - 后轴由极化活动区（ZPA）中的Shh（Sonic hedgehog）的表达限决定，后中胚层的区域发育为肢芽。

5. Shh 至少以两种方式调节趾的形成。它通过 BMP 抑制叉指间充质发挥作用，还调节软骨的增生。

6. Shh 远程增强子的突变可以通过在肢芽前缘产生第二个 ZPA 而导致多指趾畸形。

7. 背侧轴形成由 Wnt7a 在肢体外胚层的背部表达决定。

**Questions in Limb Development**• How does the forelimb grow differently other than the hindlimb?  
• What is AER, and what roles does AER play in limb development?  
• What is ZPA, and what roles does ZPA play in limb development?  
• Why do fingers form at one end of the limb and nowhere else?   
(proximal-distal axis)  
• How is it that the little finger (twinkie) develops at one edge of   
the limb and the thumb at the other? (anterior-posterior axis)  
• What’s the molecular mechanisms determining the dorsalventral axis of the limb?  
• How is the growth of three axes of tetrapod limb is coordinated?

肢体发育问题

 除了后肢，前肢的生长情况如何？

 什么是 AER，AER 在肢体发展中扮演什么角色？

 什么是 ZPA，ZPA 在四肢发展中扮演什么角色？

 为什么手指在肢体的一端和其他地方形成？（近侧 - 远侧轴线）

 小拇指（twinkie）在肢体的一个边缘发展，拇指在另一个边缘怎么发展？（前

后轴）

 什么是决定肢体背腹轴的分子机制？

 四脚肢体三轴的生长是如何协调的？

Coordinating the Three Axes

* + 1. In the limb bud, Fgf10 from mesenchyme generated by the lateral plate mesoderm   
       activates Wnt signaling in the ectoderm, which in turn induces synthesis of Fgf8 in the   
       region near the AER. Fgf8 activates Fgf10, causing a positive feedback loop.
    2. As the limb bud grows, Shh in the posterior mesenchyme creates a new signaling   
       center that induces posterior-anterior polarity, and is also activates Gremlin (Grem1)   
       to prevent mesenchymal BMPs from blocking FGF synthesis in the AER.

**三种轴极性的协调**

A. 在肢芽中，由外侧板中胚层产生的间质的 Fgf10 激活外胚层中的Wnt 信号传导，从而诱导在外胚层中 AER 附近的区域的 Fgf8 的合成。Fgf8 激活 Fgf10，导致正反馈循环。

B.随着肢芽生长，后间质中的 Shh 产生新的信号中心，诱导前后极

性，也激活 Gremlin（Grem1）以防止间质 BMP 阻断 AER 中的 FGF 合成。

**The Germ Line（生殖系）**Gametogenesis（配子发生） : the process by which the gametes (配子，sperm and egg) are formed;  
Germ cells provide the material and instructions for initiating bodies in the next generation;  
Germ line can acquire its specification either autonomously(Nanos, Vasa, Tudor, and Piwi) or by induction.  
Germ cells usually do not arise within the gonads. Rather, the gamete progenitor cells - the primordial germ cells (原始生殖细胞, PGCs) - arise elsewhere and migrate into the developing gonads.

生殖系（Germ Line）

配子发生（Gametogenesis）：形成配子(gametes，sperm and egg 精子和卵子)的过程;

生殖细胞提供材料和指令，用于启动下一代的生成;

生殖系可以自主获得特化（Nanos，Vasa，Tudor 和 Piwi）或通过感应。

生殖细胞通常不会在性腺内出现。相反，生殖细胞祖细胞-原始生殖细胞（the primordial germ cells ，PGC）-在其他地方出现，然后迁移到发展中性腺。

Transcriptional silencing is critical for preventing the germ line from   
differentiating into somatic cells, and germ cell differentiation cannot   
commence until the disappearance of PIE-1 in later embryonic stages.

转录沉默对于防止胚系分化成体细胞是至关重要的，直到 PIE-1 在胚胎晚期阶段消失 才能开始生殖细胞分化。

**Germ Cell Determination in Drosophila**

Pole cells are surrounded by the pole plasm (germ plasm), a complex collection of mitochondria, fibrils, and polar granules that contain translational regulators such as Vasa, Tudor, and Piwi family proteins. The germ plasm is entirely sufficient for inducing germ cells.

Formation of germ cells where Vasa is released from the cell cortex and accumulates around the microtubules organized by the mitotic centrosomes.

果蝇中的生殖细胞决定

极细胞（Pole cells）被**极性质粒（生殖质）**包围，线粒体，原纤维和极性颗粒的复杂集合包含翻译调控因子，如 Vasa，Tudor 和 Piwi 家族蛋白。 生殖质完全足以诱导生殖细胞。

Vasa 从细胞皮层释放并在有丝分裂中心体组织的微管周围累积，这是生殖细胞的形成的位置。

**Germ Cell Determination in Mammals**

In mammals, germ cells are induced in the embryo  
In mice, the germ cells form at the posterior region of the epiblast, posterior   
proximal epiblast, at the junction of the extraembryonic ectoderm, epiblast,   
primitive streak, and allantois (尿囊).

在哺乳动物中，生殖细胞在胚胎中被诱导

在小鼠中，生殖细胞形成于外胚层后部，后近端外胚层（posterior proximal epiblast），在 胚外外胚层，外胚层，原条和尿囊的交界处

**Germ Cell Migration in Drosophila**

Germ cells migration in Drosophila occurs in several steps involving trans-epithelial migration, repulsion from the endoderm, and attraction to the gonads.

Hub cells secrete Unpaired to activate the JAK-STAT pathway in the   
adjacent germ stem cells to specify their self-renewal.

果蝇中的生殖细胞迁移发生在几个涉及跨上皮迁移，内胚层排斥和对性腺的吸引的步骤中。

Hub 细胞分泌不配对以激活相邻生殖干细胞中的 JAK-STAT 途径以指定其自我更新。

**Germ Cell Migration in Mammals**

**The PGCs migrate through the gut and, dorsally, into the   
genital ridges (生殖嵴）**

**PGCs 通过肠道和背部迁移进入生殖嵴**

**Meiosis - 减数分裂**• Meisosis is initiated and regulated by signals from the gonad (性腺).  
• Meiotic cells undergo two cell divisions without an intervening period of DNA   
replication. (from diploid to haploid)  
• Homologous chromosomes joined at a kinetochore (动粒) pair together and   
recombine genetic material.

减数分裂

 减数分裂是由性腺（gonad）的信号启动和调节的。

 减数分裂细胞经历两次细胞分裂， 中间阶段 DNA 不复制。（从二倍体到单倍体）

 同源染色体在动粒（kinetochore）成对连接，重组遗传物质。

**Oogenesis - 卵子发生**  
Constructing the egg involves   
• Making the nucleus haploid  
• Building the organelles (细胞器) involved in fertilization;  
• Synthesizing and positioning the mRNAs and proteins used in early development;   
• Accumulating energy sources and energy producing organelles (ribosomes, yolk, and mitochondria) in the cytoplasm.

制造核单倍体

构建细胞器（organelles）参与受精

合成和定位早期发育中使用的 mRNA 和蛋白质 ;

在细胞质中积累能量来源和能量产生细胞器（核糖体，卵黄和线粒体）。

**.哺乳动物的配子发生**

迁徙到生殖腺的 PGCs 不会自己决定成为精子还是卵子。这是他们所居住的性腺决定的。

最基本的一组信号调节减数分裂的时间，这些信号包括 Wnt4 和视黄酸（retinoic acid）。

**雌性卵子发生**

减数分裂在有限的细胞群中启动一次

每个减数分裂产生一个配子

减数分裂的完成延迟数月或数年

减数分裂症在第一次减数分裂前期被抑制，并在较小的细胞群中重新开始

配子的分化发生在第一个减数分裂前期的二倍体

所有染色体在减数分裂前期都表现出相同的转录和重组

**雄性精子发生**

在有丝分裂的干细胞群体中持续发生减数分裂

每个减数分裂产生四个配子

减数分裂在几天或几周内完成

减数分裂和分化持续进行，没有细胞周期阻滞

配子的分化发生在单倍体，减数分裂结束后

在减数分裂前期，性染色体被排除在重组和转录之外

**（RA）决定哺乳动物生殖细胞减数分裂和性分化的时机**

**Spermatogenesis （精子发生）- Three Major Phases 三个主要阶段**

开始于青春期并发生在支持细胞（the Sertoli cells）之间的隐窝（recesses）中

1、Proliferation of spermatogonia (精原细胞)- 精子干细胞的增殖

2、减数分裂阶段 - 创建单倍体状态

3、减数分裂后“成形期”（“shaping” phase）- spermiogenesis /精子形成：圆形细胞（spermatids/精子细胞）把驱除它们的细胞质变成了流线型的精子

**A Mature Sperm**

• The construction of the acrosomal vesicles from the Golgi apparatus.  
• Rotation of the nucleus. The nucleus flattens and condenses, the remaining cytoplasm is jettisoned (丢弃), and the mitochondria form a ring around   
the base of the flagellum (鞭毛）.  
• Remodeling of nucleosomes -the histones of the haploid nucleus are replaced by   
protamines (鱼精蛋白）

**成熟的精子**

 来自高尔基体的顶体囊泡

 核的旋转。细胞核变平和凝聚，剩余的细胞质丢弃（jettisoned），和线粒体围绕鞭毛

（flagellum）的基部形成一个环。

 核小体重塑-单倍体细胞核的组蛋白被替换为鱼精蛋白（protamines）

**Mammalian Oogenesis /卵子发生**The eggs mature through an intricate coordination of hormones/全身激素, paracrine factors/旁分泌因子, and tissue anatomy/组织解剖结构.

卵子成熟的通过一个由 hormones/全身激素,paracrine factors/旁分泌因子, and tissue anatomy/组织解剖结构构成的错综复杂的协调

**Quiz**• What are PGCs?   
• What is germ plasm? What are the roles of germ plasm?  
• What are the key components for constituting a functional oocyte?  
• What are shared features and differences between male and female gametogenesis in mammals?  
• The major steps for spermatogenesis.  
• The factors required for normal oogenesis.

 什么是 PGC？

 什么是生殖质？种质有什么作用？

 什么是构成功能性卵母细胞的关键组成部分？

 哺乳动物雄性和雌性配子形成的共同特征和差异是什么？

 精子发生的主要步骤。

 正常卵子发生所需的因素。 整理 by Levi &花花