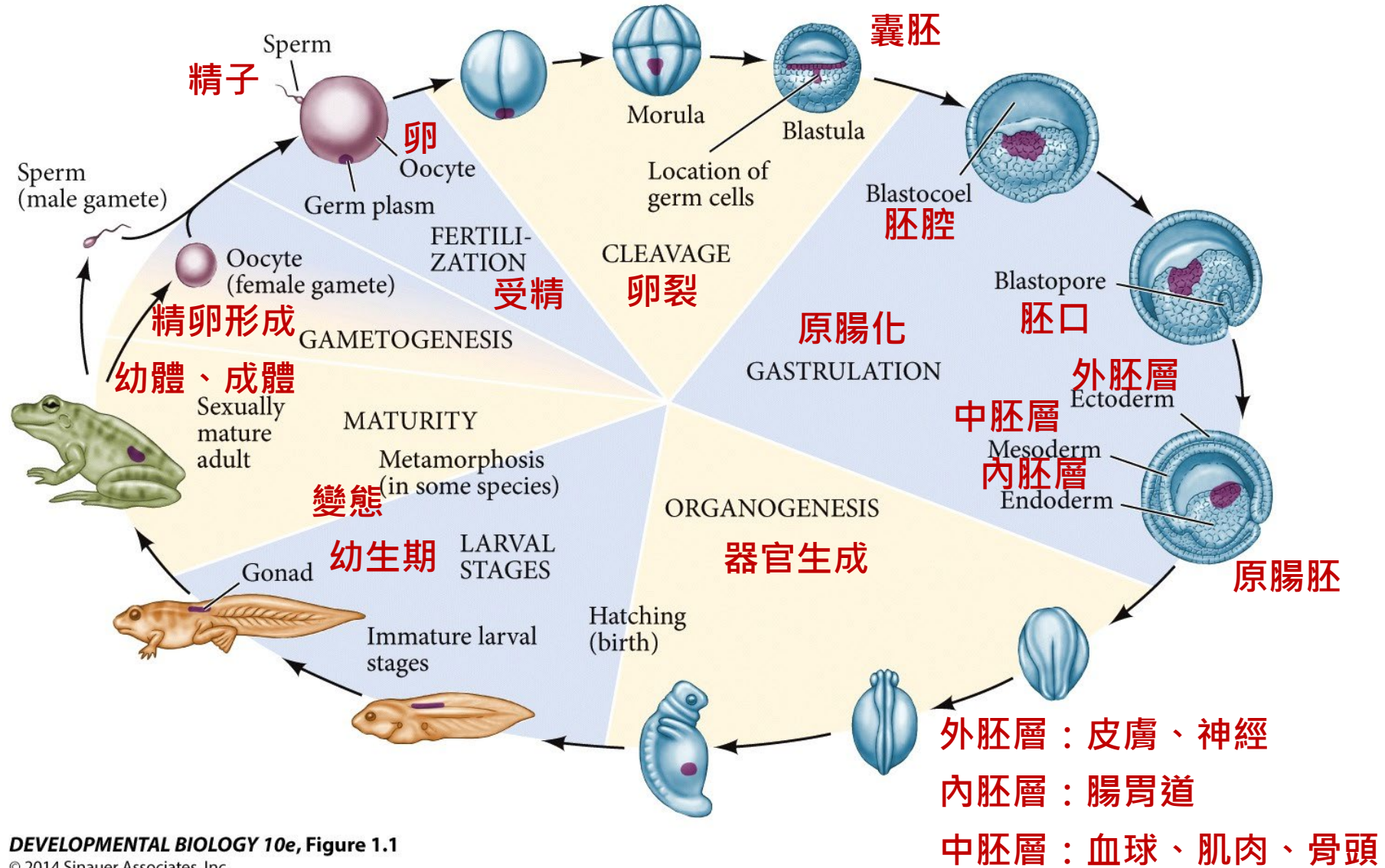


# 動物發育與基因調控

中央研究院  
細胞與個體生物學研究所  
蘇怡璇

**動物發育生物學在研究什麼？**

# 動物發育生物學在研究 動物由單細胞受精卵長成多細胞個體的過程



動物發育生物學常用的模式物種有哪些？

The Big Six

# 動物發育生物學常用的模式物種

線蟲



果蠅



海鞘



斑馬魚



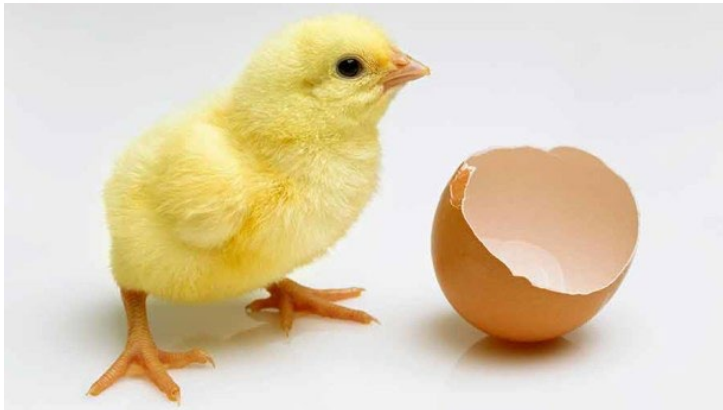
蟾蜍



海膽



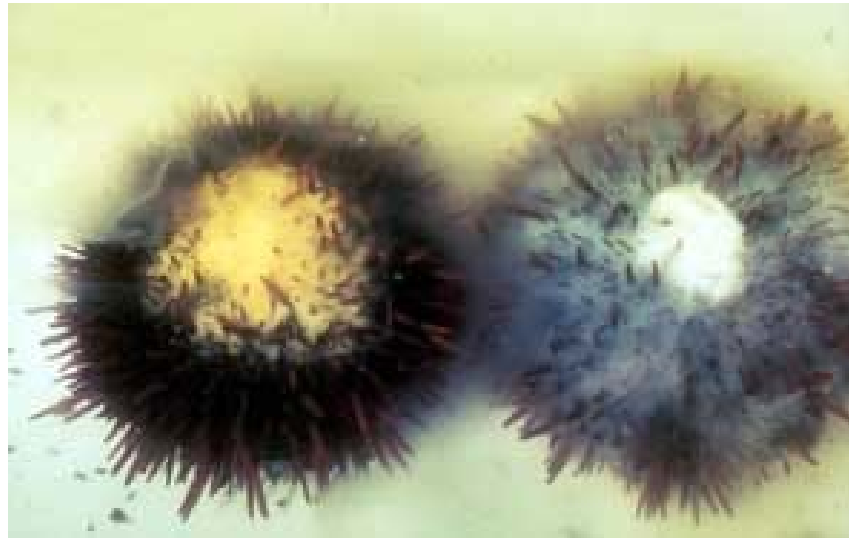
雞



老鼠

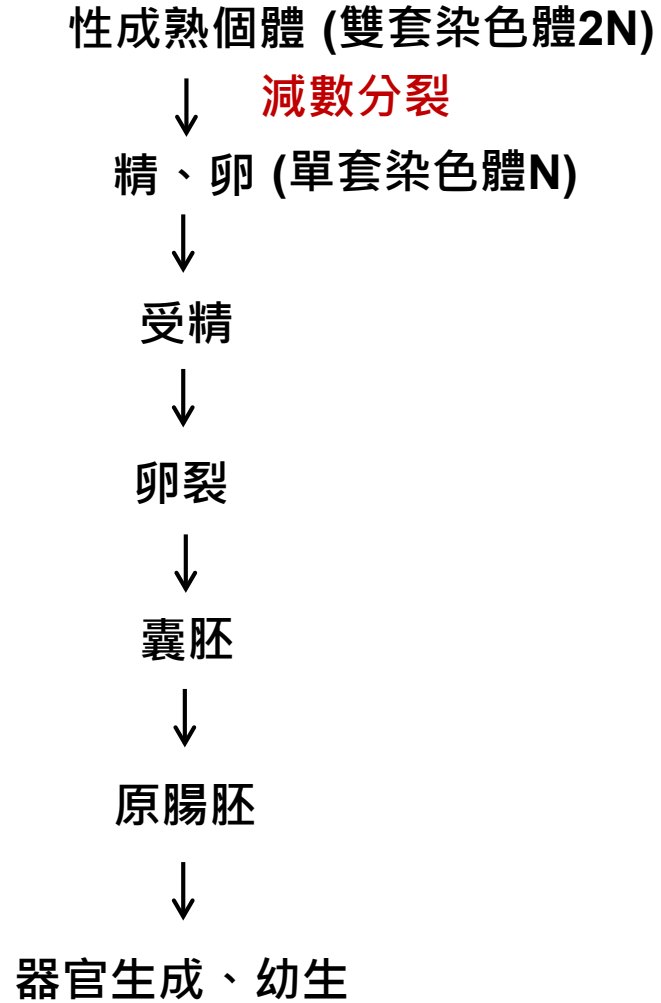


# 海膽能產出大量精卵，是研究胚胎發育的好材料

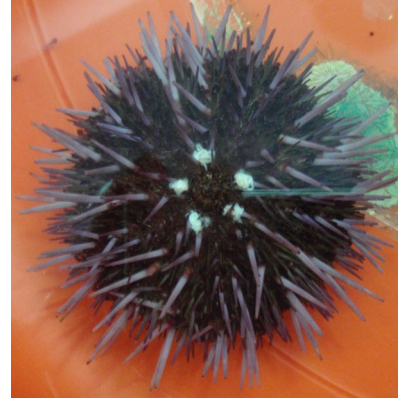


3百萬個卵子/ml  
4百億個精子/ml

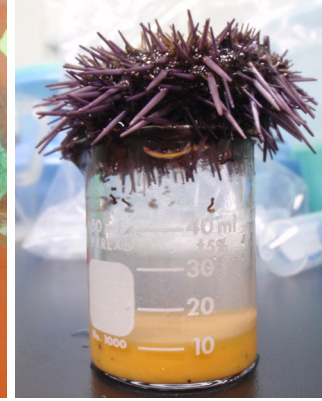
# 早期胚胎發育過程



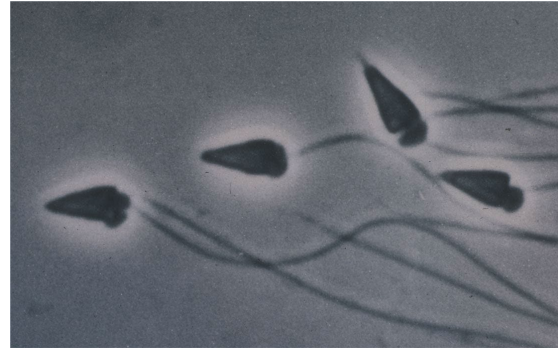
公海膽



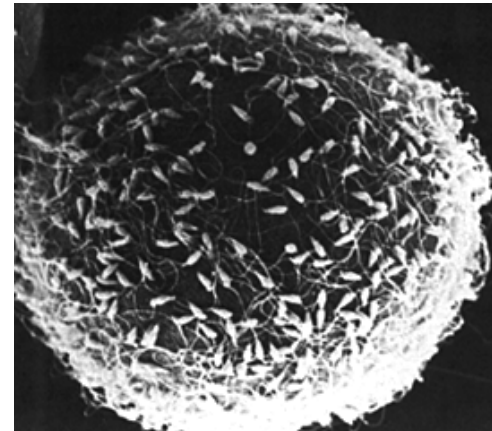
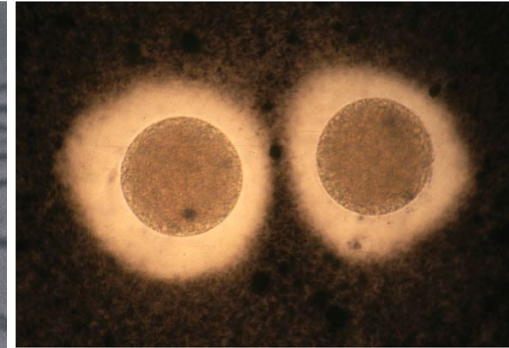
母海膽



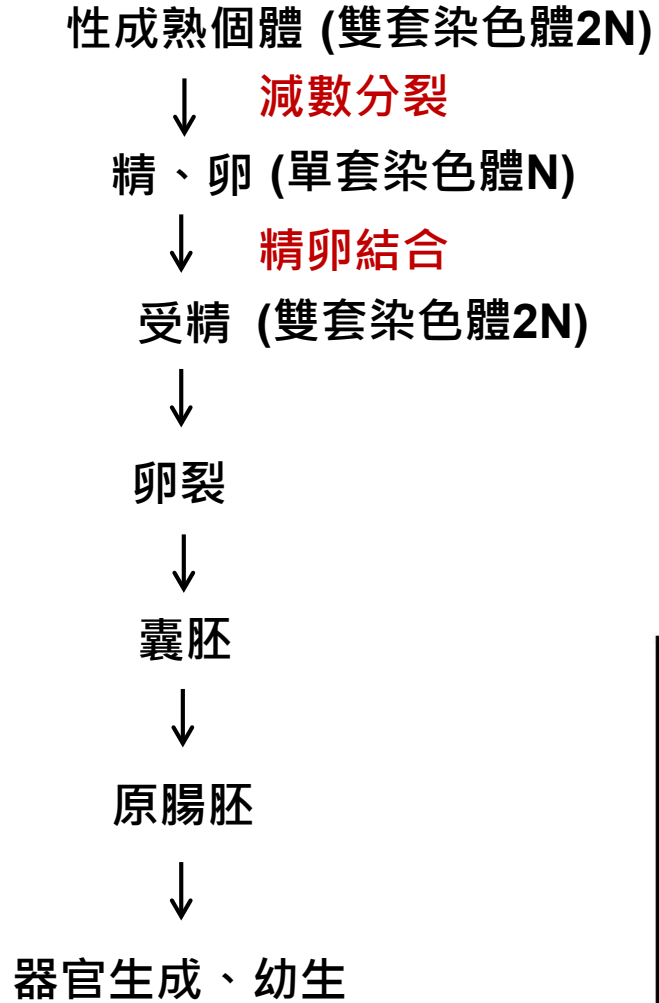
海膽精子



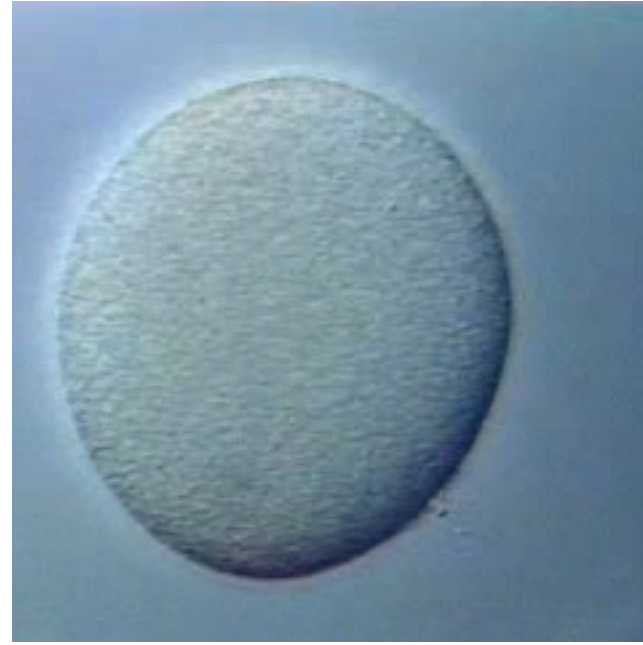
海膽卵子



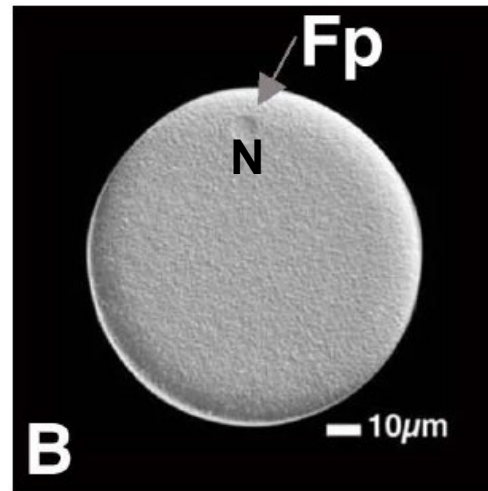
# 早期胚胎發育過程



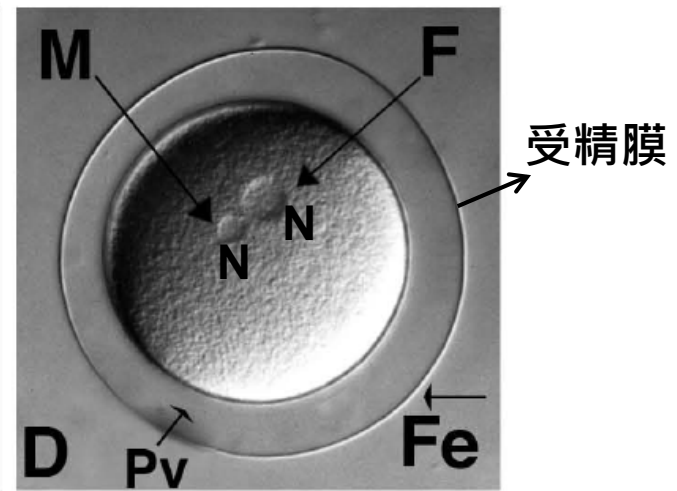
海膽的受精



未受精卵

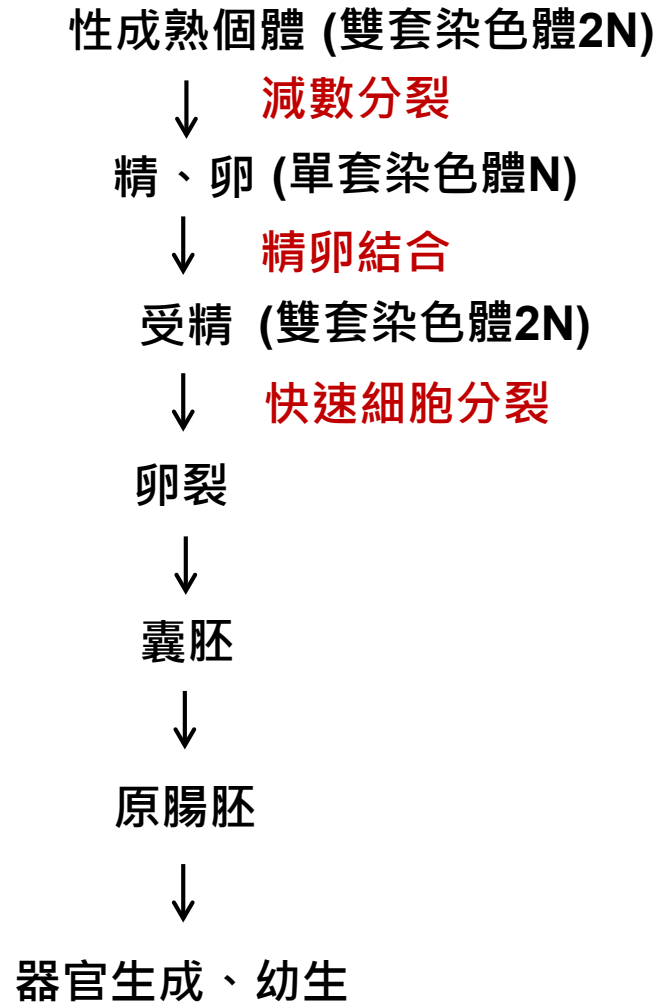


受精卵





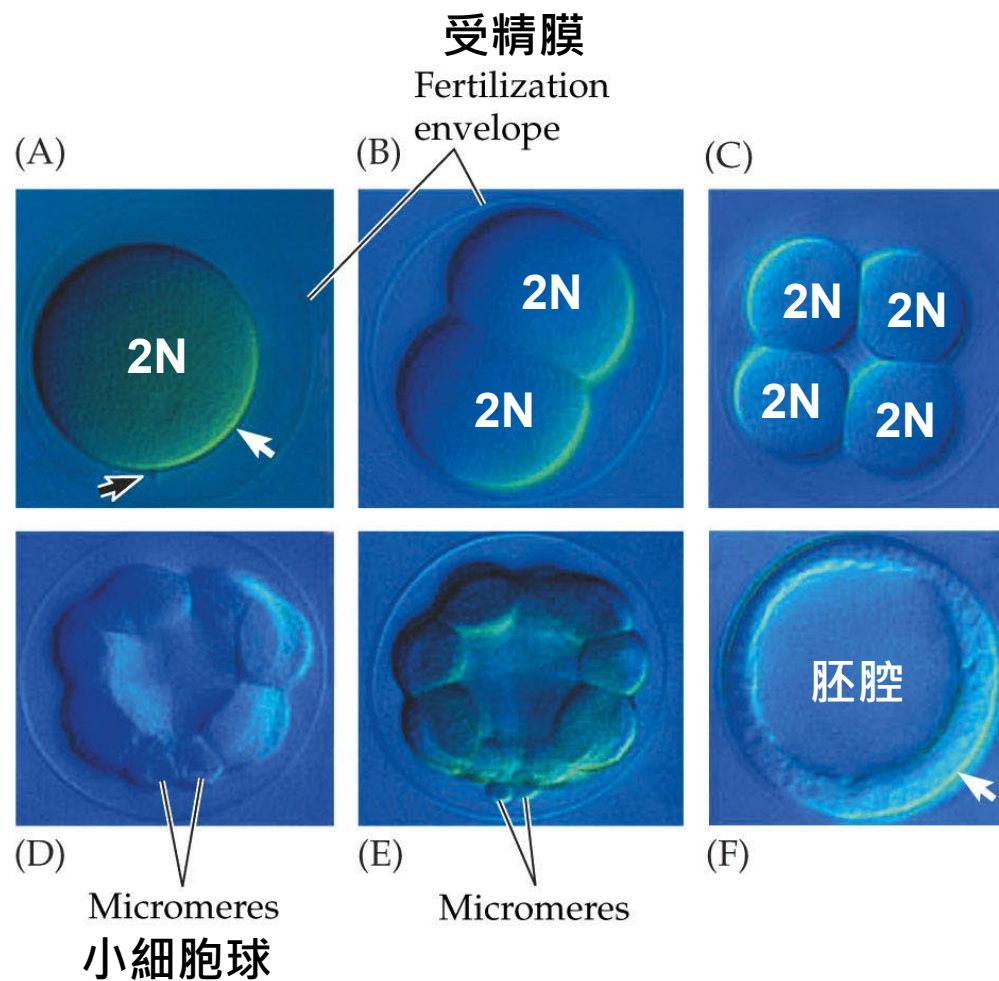
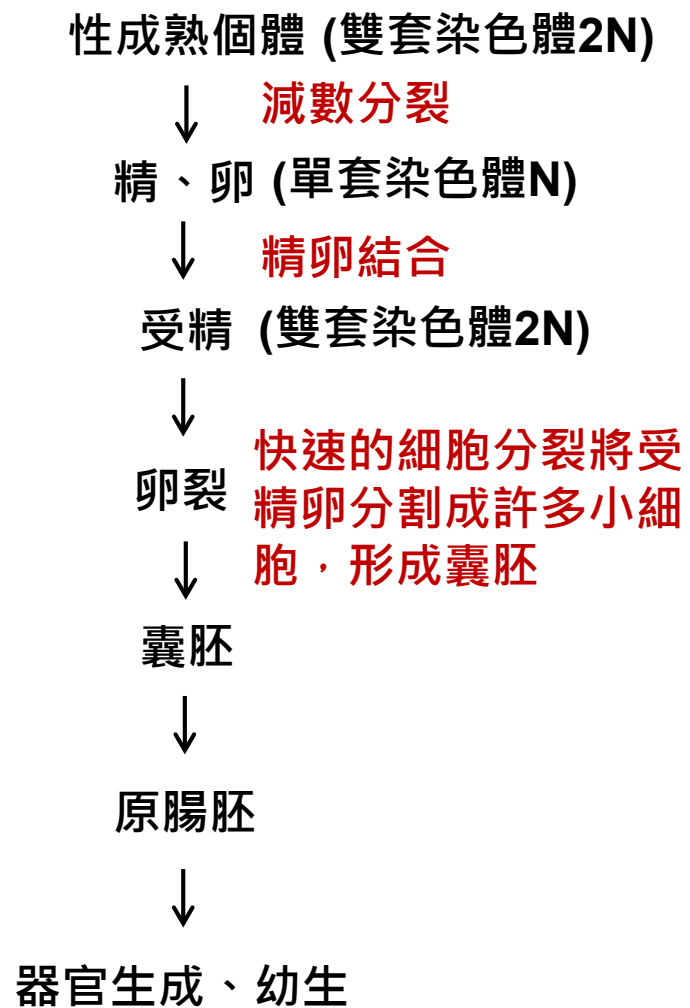
# 早期胚胎發育過程



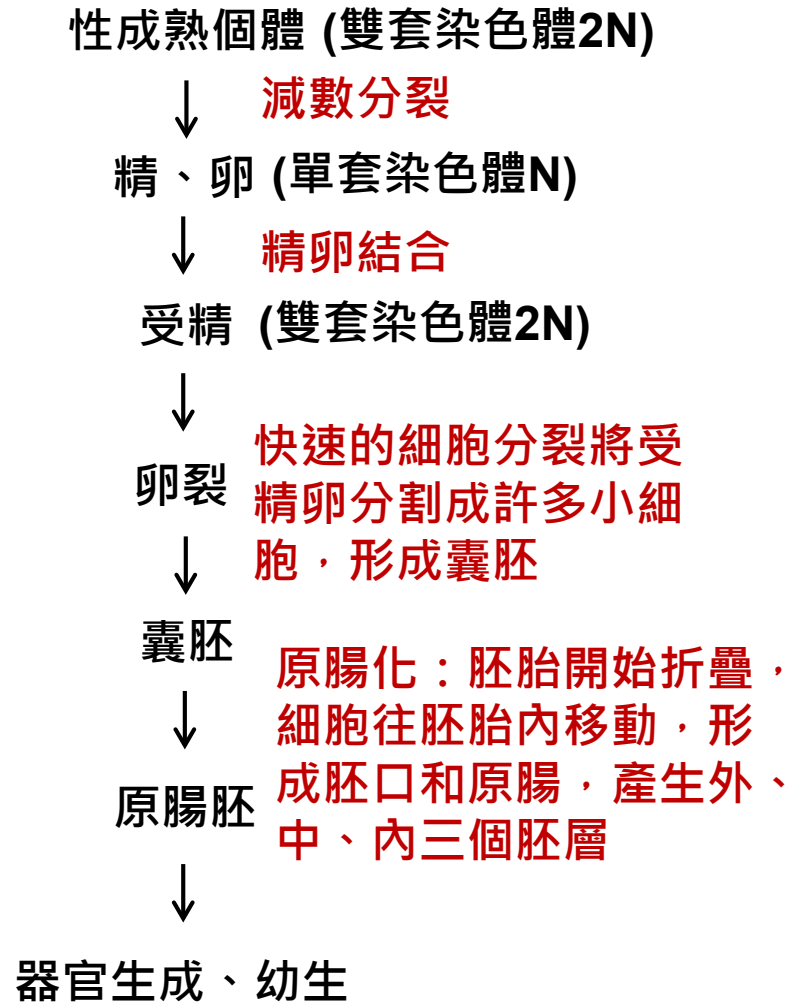
海膽的卵裂



# 早期胚胎發育過程



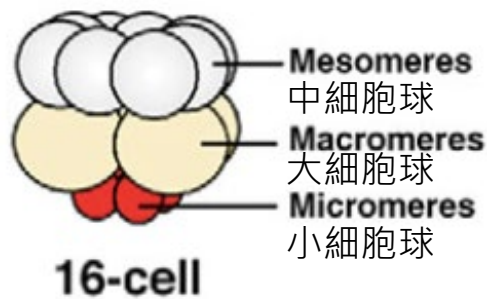
# 早期胚胎發育過程



海膽的原腸胚形成

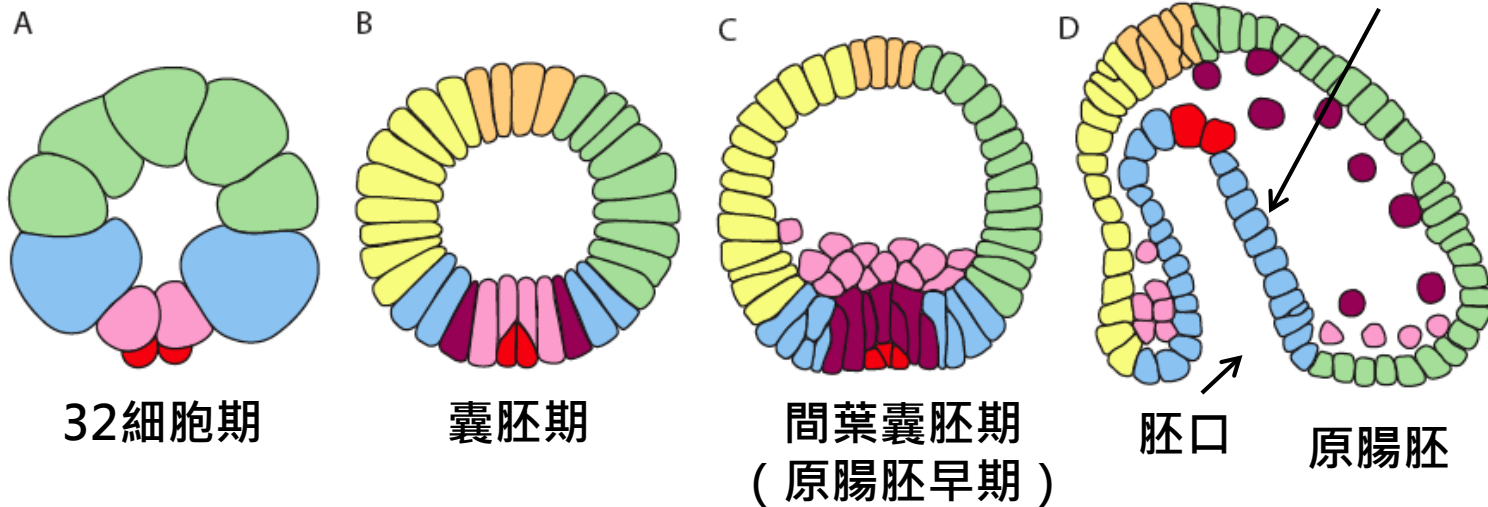


# 海膽的早期發育

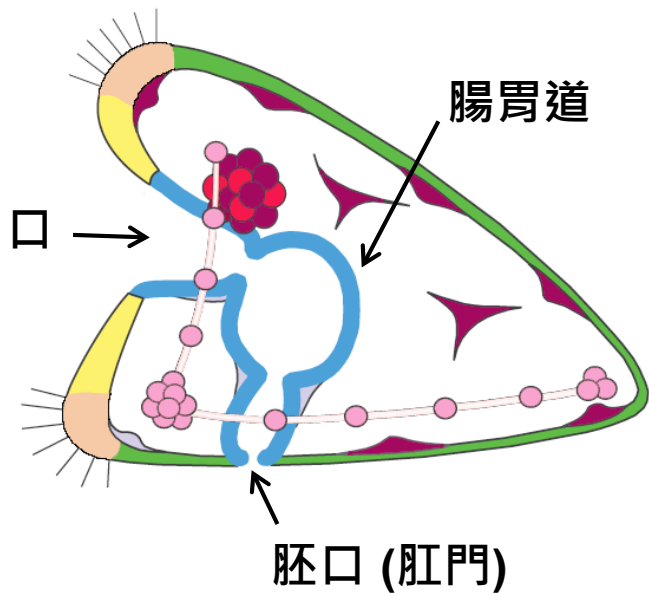


16-cell

16細胞期

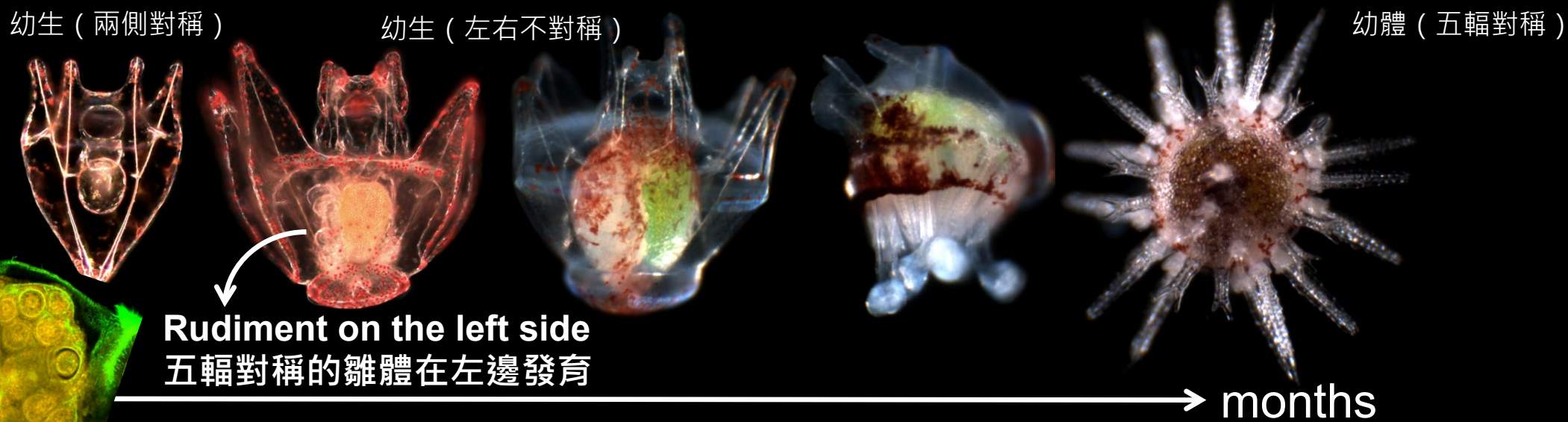
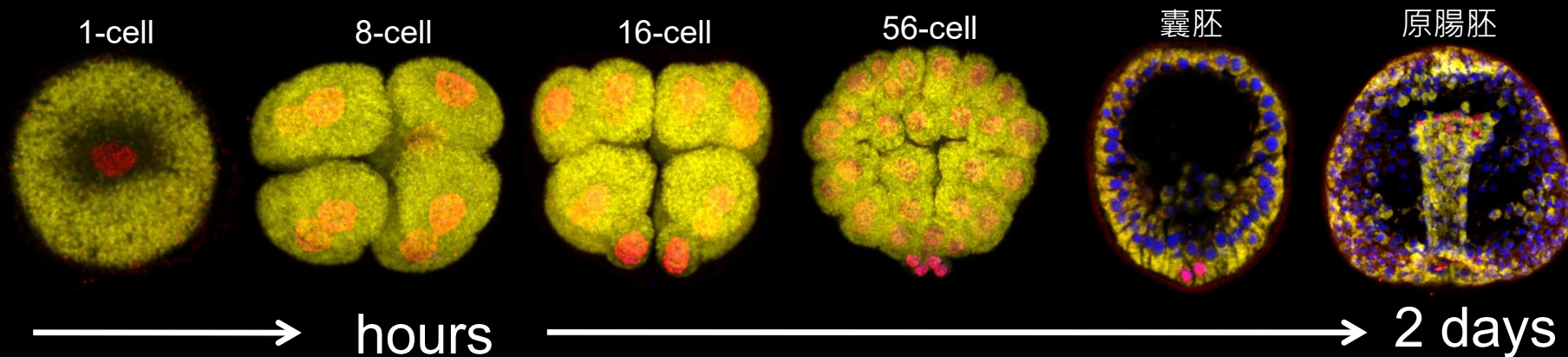


原腸胚晚期  
(早期幼生)



- 口面外胚層
  - 反口面外胚層
  - 纖毛帶
  - 內胚層
  - 骨骼中胚層
  - 植物板中胚層
  - 先驅生殖細胞
  - ／ 骨針
- 外胚層  
內胚層  
中胚層

# 海膽的胚胎發育與變態



# 胚胎發育的多樣性

線蟲



果蠅



海鞘



斑馬魚



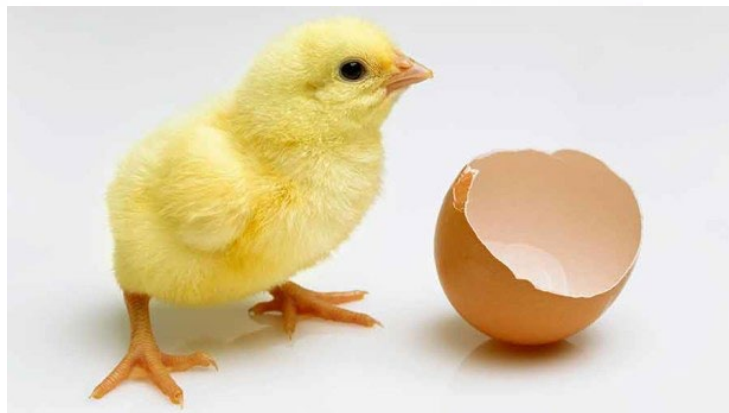
蟾蜍



海膽



雞



老鼠



# 不同動物有不同的卵裂模式

## I. 完全分裂

### A. 卵黃含量少且分布平均

#### 1. 輻射分裂

(如: 海膽、文昌魚)

#### 2. 螺旋分裂

(如: 沙蠶、貝類、扁蟲)

#### 3. 兩側分裂

(如: 海鞘)

#### 4. 旋轉分裂

(如: 哺乳類、線蟲)

### B. 卵黃含量中等

#### 偏移的輻射分裂

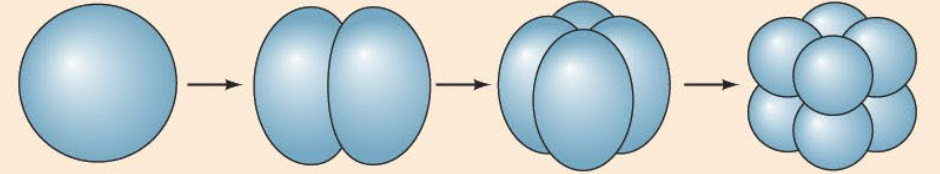
(如: 兩生類)

## I. HOLOBLASTIC CLEAVAGE

### A. Isolecithal

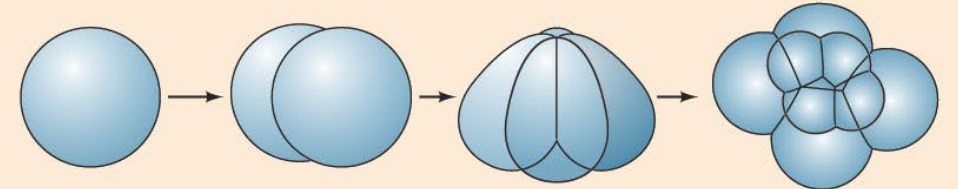
#### 1. Radial cleavage

Echinoderms,  
amphioxus



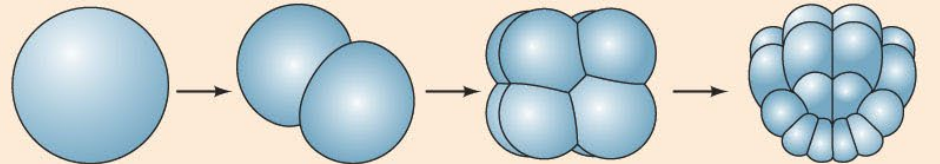
#### 2. Spiral cleavage

Annelids, molluscs,  
flatworms



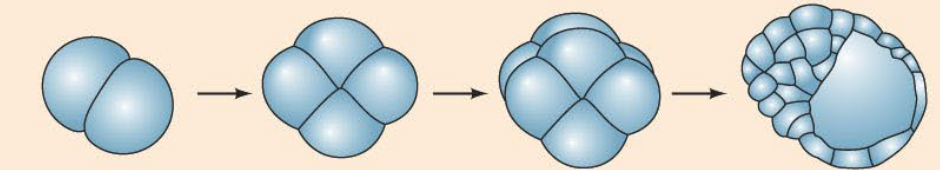
#### 3. Bilateral cleavage

Tunicates



#### 4. Rotational cleavage

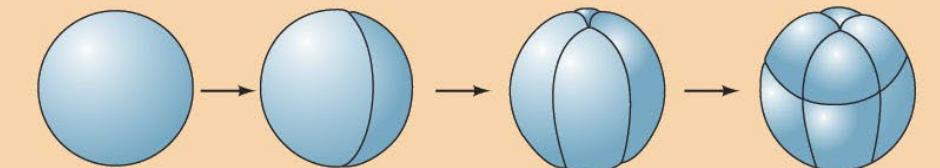
Mammals, nematodes



### B. Mesolecithal

#### Displaced radial cleavage

Amphibians



# 不同動物有不同的卵裂模式

## II. 不完全分裂

### A. 卵黃分布在一端

1. 兩側分裂  
(如: 頭足類)

2. 盤狀分裂  
(如: 魚類、爬蟲類、鳥類)

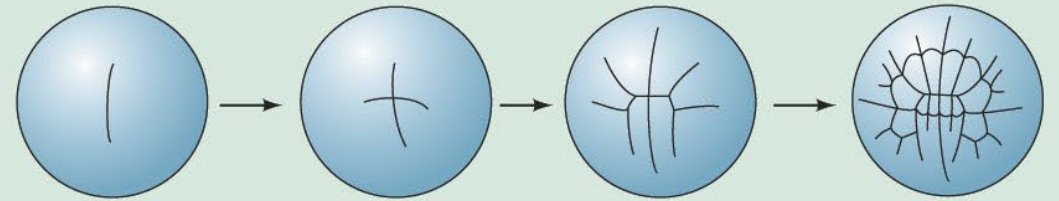
### B. 卵黃分布於中央

表面分裂  
(如: 昆蟲)

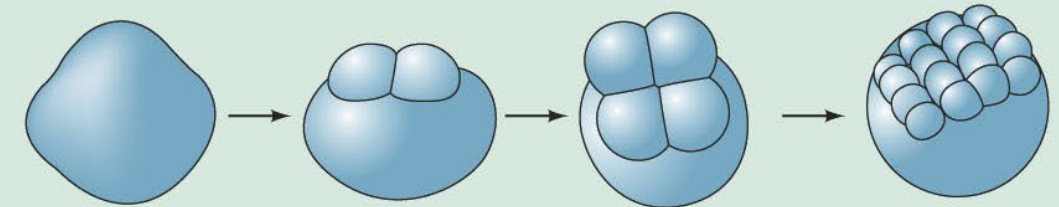
## II. MEROBLASTIC CLEAVAGE

### A. Telolecithal

1. Bilateral cleavage  
Cephalopod  
molluscs

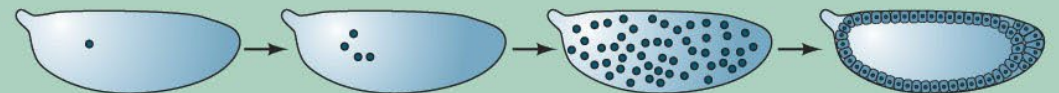


2. Discoidal cleavage  
Fish, reptiles, birds



### B. Centrolecithal

Superficial cleavage  
Most insects

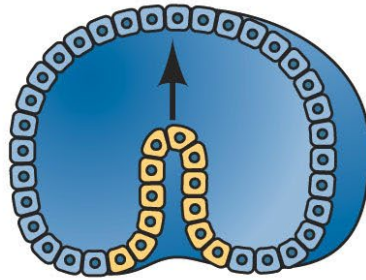




# 不同動物利用不同的(一種或數種)細胞移動方式進行原腸化

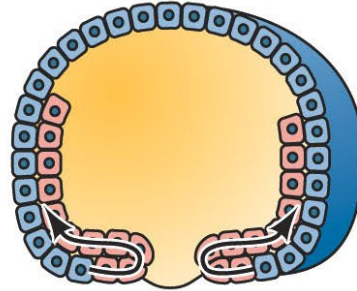
一個區域的細胞向  
空腔內凹陷

**Invagination**



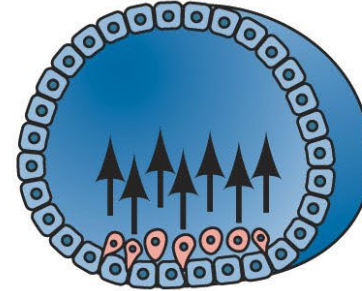
外層細胞向內貼  
著內壁散佈

**Involution**



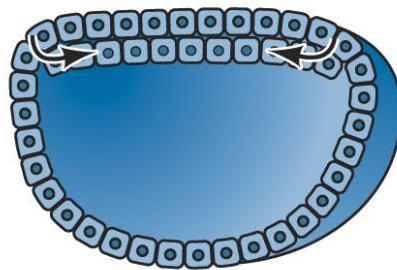
個別細胞改變形狀  
向空腔內移動

**Ingression**



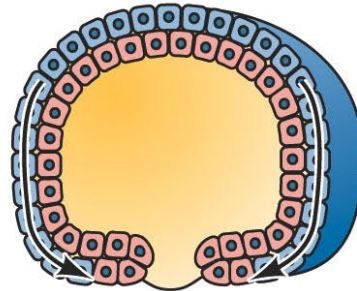
單層細胞分成多層細胞

**Delamination**

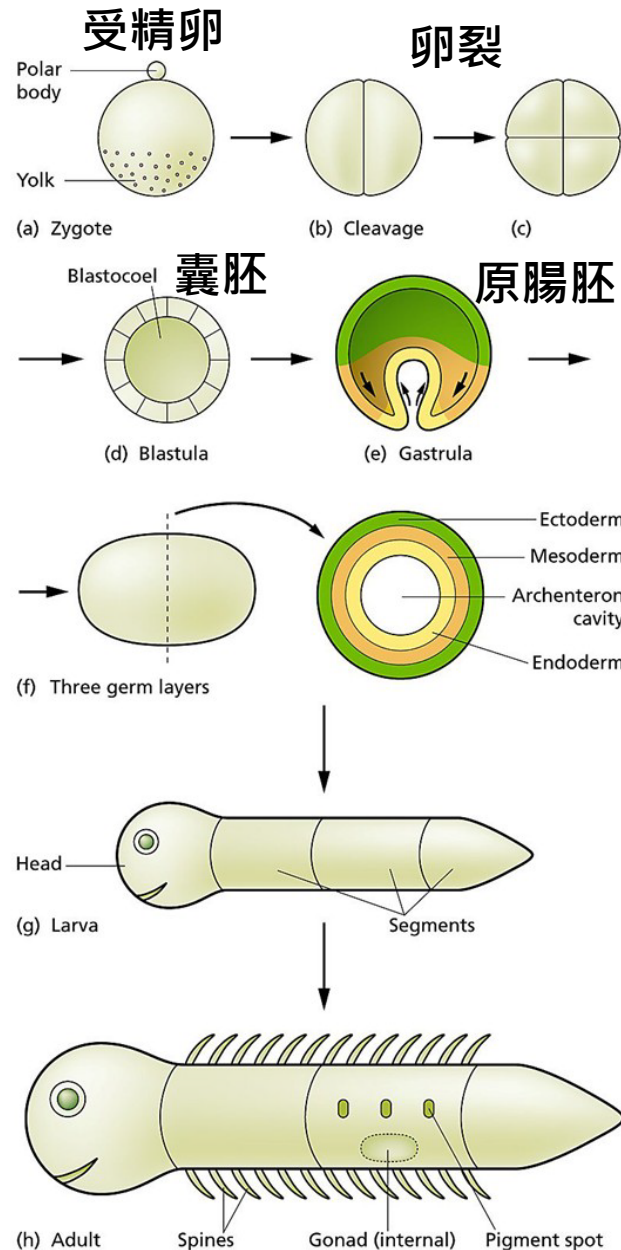
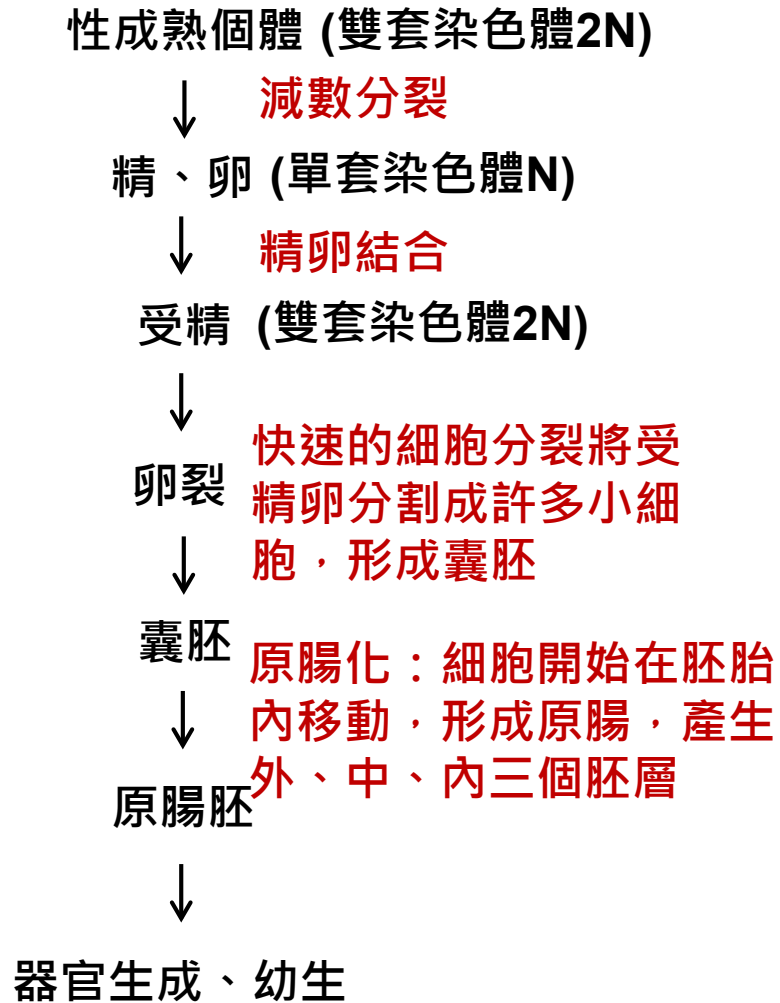


外層細胞延伸包覆  
胚胎其他部分

**Epiboly**



# 早期胚胎發育過程



**三胚層-**  
 外胚層:皮膚、神經  
 內胚層:腸胃道  
 中胚層:血球、肌肉、骨頭

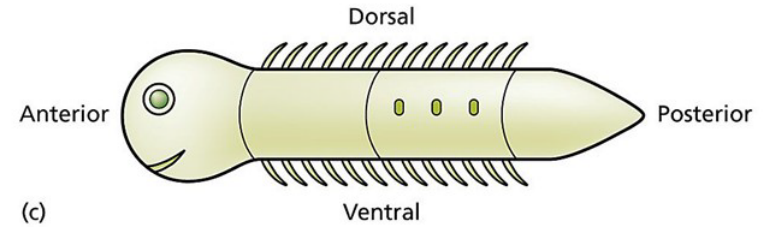
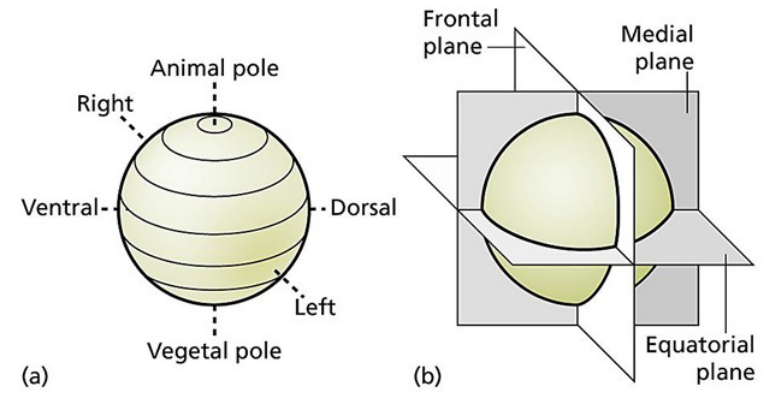
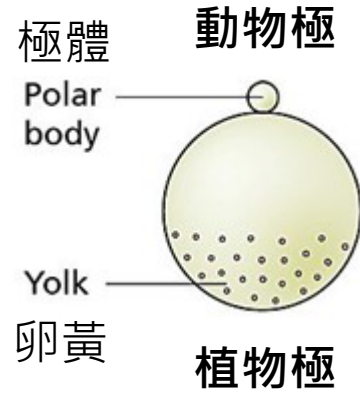
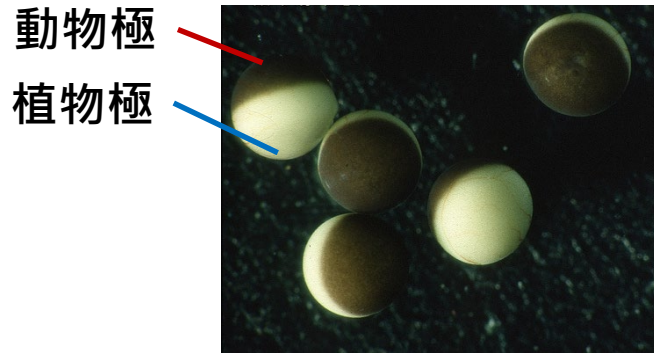
**三胚層動物 (兩側對稱)**

**VS.**

**兩胚層動物 (水母、水螅、櫛水母)**

# 動物身體體軸的建立

卵（受精卵、早期胚胎）的極性



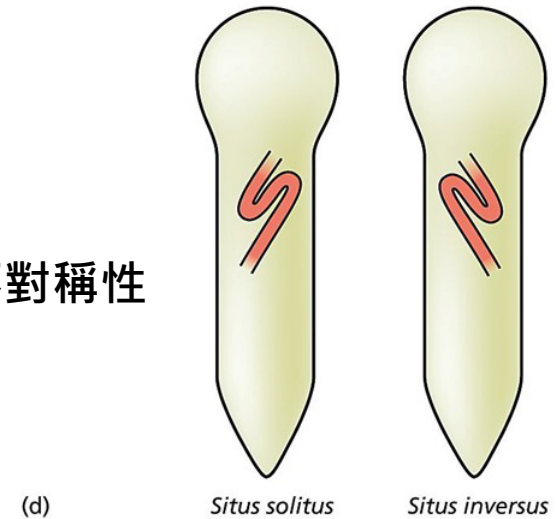
兩側對稱動物胚胎的三個體軸

前後軸、頭尾軸

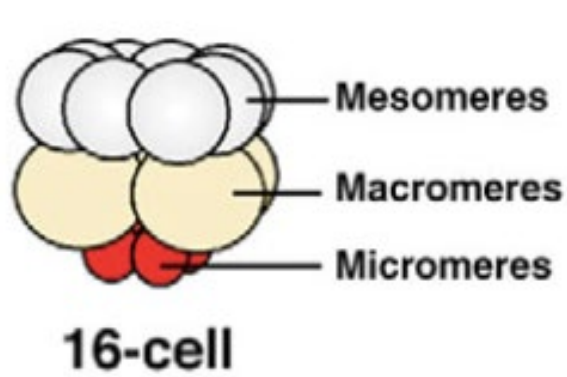
背腹軸

左右軸

左右不對稱性

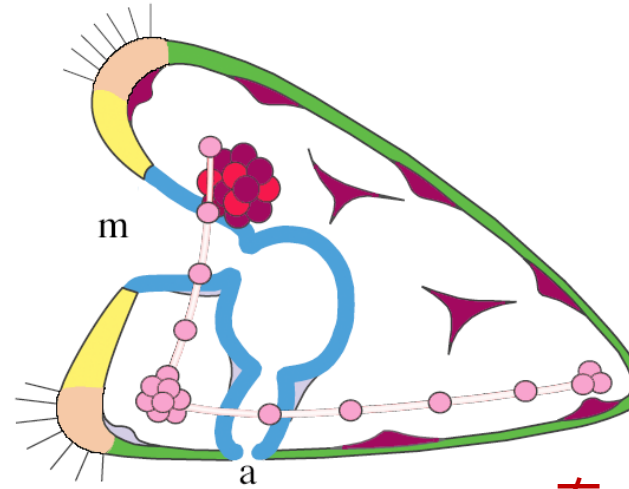


# 海膽與人類胚胎的極性與體軸



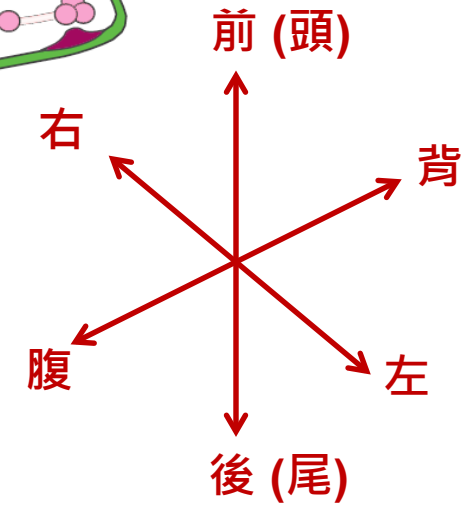
動物極  
植物極

A vertical red double-headed arrow indicates the polarity of the embryo, with '動物極' (Animal pole) at the top and '植物極' (Vegetal pole) at the bottom.



外胚層位於動物極  
中、內胚層位於植物極  
原腸化從植物極開始進行

外胚層位於動物極  
中、內胚層位於植物極  
原腸化從植物極開始進行



# 發育生物學的發展史



亞里斯多德  
Aristotle (384-322 BC)

種子與土壤的概念  
"Seed and Soil" concept of reproduction



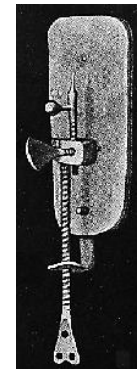
威廉·哈維 英國醫生  
William Harvey (1578-1657)

所有動物由卵發育而來  
EX OVO OMNIA  
(Everything comes from an egg)



雷文霍克  
Anton Van Leeuwenhoek (1632-1723)

發現精子 (精蟲)  
The discovery of sperm (1677)  
Spermatozoa "sperm animals"  
"Sperm were seeds (sperm/semen=seed) and that the female merely provided the nutrient soil into which the seeds were planted." (1685, Leeuwenhoek)





尼古拉斯·哈佐克 荷蘭的數學家和物理學家

Nicolas Hartsoeker (1656-1725)

精子裡的小人

A preformed human "Homunculus" within the human sperm (1694)

精子很重要

Lazzaro Spallanzani (1729-1799)

Filtered toad semen would not fertilize eggs.

Prevost & Dumas (1824)

Sperm were not parasites but rather the active agents of fertilization.

A. von Kolliker (1840s)

Description of the formation of sperm from cells within the adult testes.

精子和卵都很重要

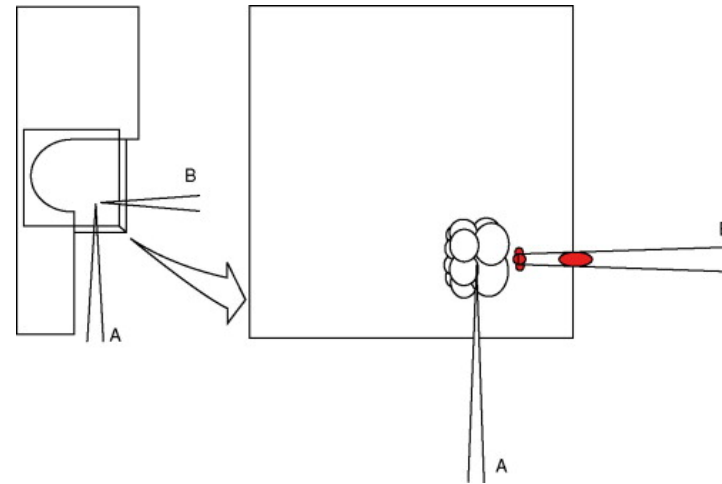
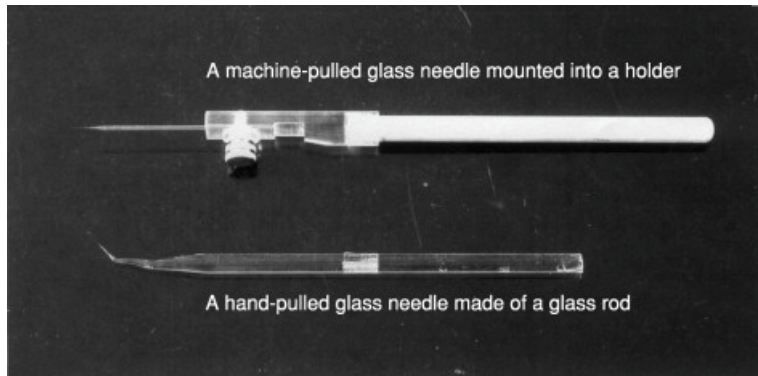
Oscar Hertwig & Herman Fol (1876)

First observation of fertilization in sea urchins and sea stars.

# 發育生物學的發展史

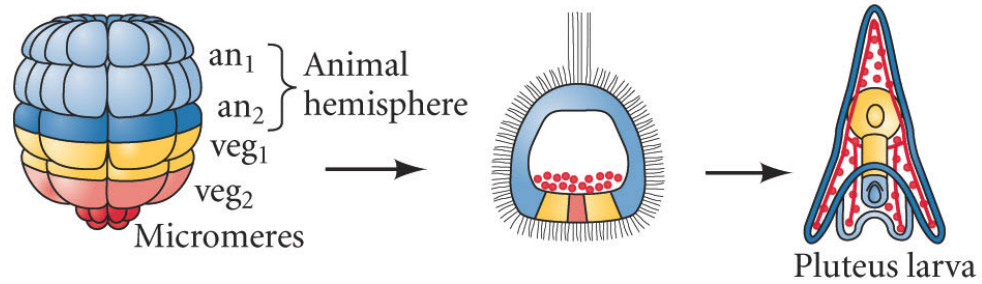
**描述性的胚胎學** – 以顯微鏡觀察並描述各種動物的發育過程

**實驗胚胎學** – 二十世紀初胚胎學家利用顯微手術操弄胚胎  
( 主要是用海膽胚胎和蛙胚 ) 以了解胚胎發育的機制



# 實驗胚胎學 – “剪下”與“貼上”的實驗

(A) Normal development

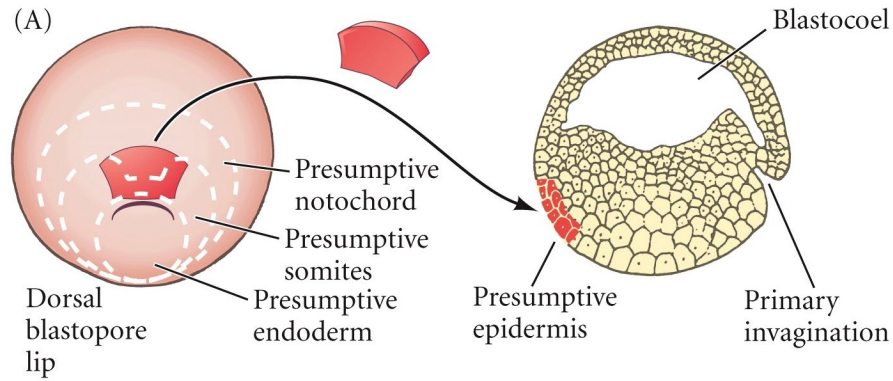


正常的海膽發育

實驗結論：海膽胚胎的小細胞球具有**誘導**其他細胞改變命運的能力



# 實驗胚胎學 – “剪下”與“貼上”的實驗



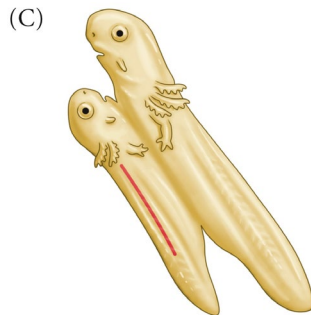
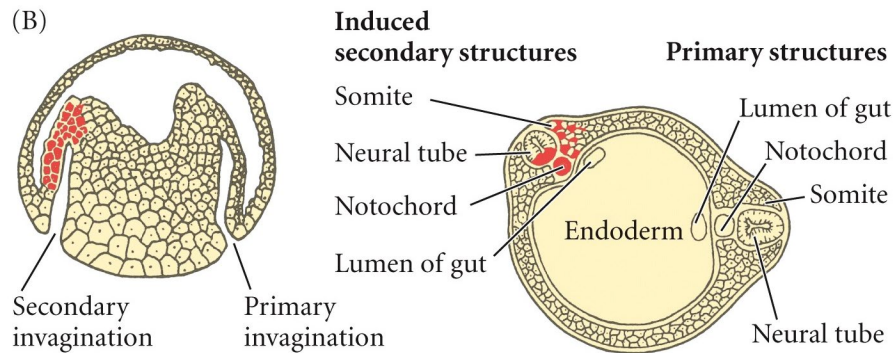
## The Nobel Prize in Physiology or Medicine 1935



Hans Spemann  
Prize share: 1/1

The Nobel Prize in Physiology or Medicine 1935 was awarded to Hans Spemann "for his discovery of the organizer effect in embryonic development".

Photos: Copyright © The Nobel Foundation



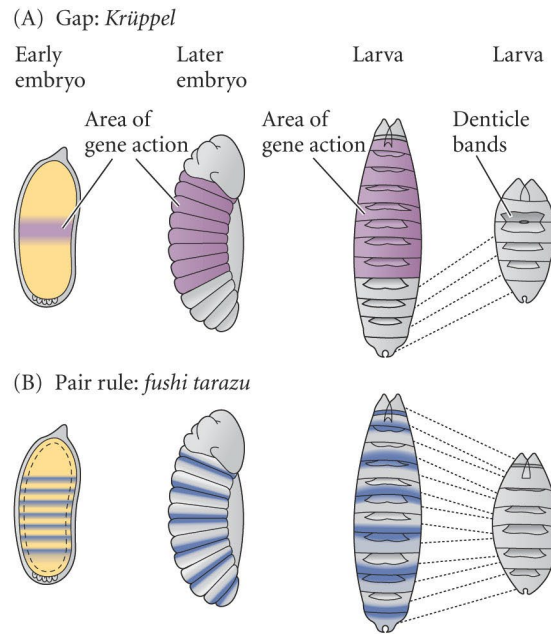
實驗結論：蝾螈胚胎胚口的背面細胞具有**誘導**其他細胞改變命運的能力

# 發育生物學的發展史

**描述性的胚胎學** – 以顯微鏡觀察並描述各種動物的發育過程

**實驗胚胎學** – 二十世紀初胚胎學家利用顯微手術操弄胚胎 (主要是用海膽胚胎和蛙胚) 以了解胚胎發育的機制

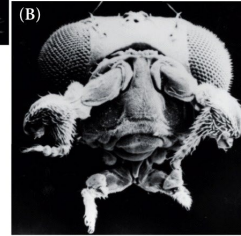
**發育遺傳學** – 利用突變的果蠅來篩選與發育相關的性狀



觸角  
↓  
腳



平衡桿  
↓  
翅膀



DEVELOPMENTAL BIOLOGY 10e, Figure 6.38  
© 2014 Sinauer Associates, Inc.

# The Nobel Prize in Physiology or Medicine 1995



Edward B. Lewis  
Prize share: 1/3



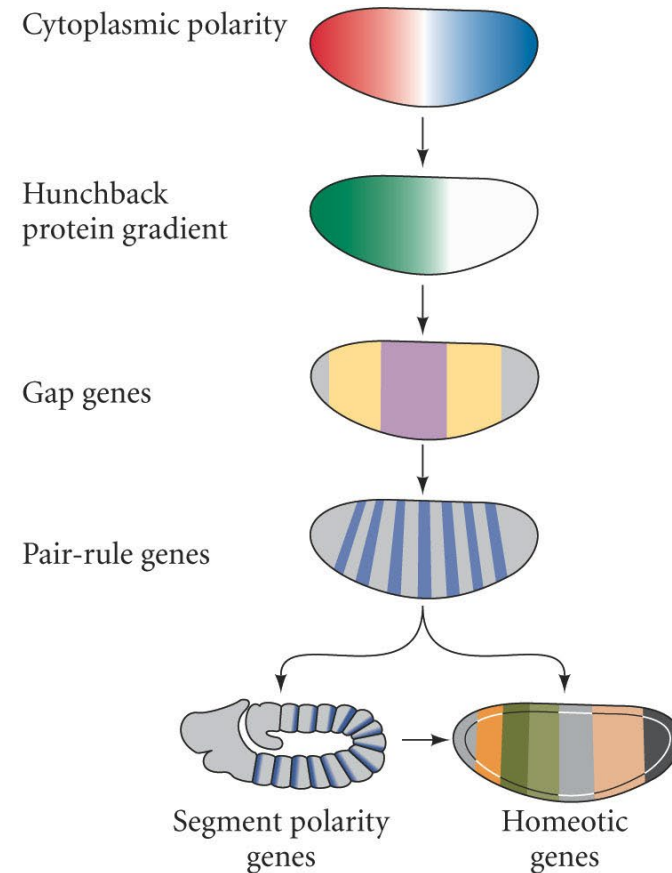
Christiane Nüsslein-Volhard  
Prize share: 1/3



Eric F. Wieschaus  
Prize share: 1/3

The Nobel Prize in Physiology or Medicine 1995 was awarded jointly to Edward B. Lewis, Christiane Nüsslein-Volhard and Eric F. Wieschaus "for their discoveries concerning the genetic control of early embryonic development".

Photos: Copyright © The Nobel Foundation



# The Nobel Prize in Physiology or Medicine 2001



Leland H. Hartwell  
Prize share: 1/3



Tim Hunt  
Prize share: 1/3



Sir Paul M. Nurse  
Prize share: 1/3

The Nobel Prize in Physiology or Medicine 2001 was awarded jointly to Leland H. Hartwell, Tim Hunt and Sir Paul M. Nurse *"for their discoveries of key regulators of the cell cycle"*.

Photos: Copyright © The Nobel Foundation



# The Nobel Prize in Physiology or Medicine 2002



Sydney Brenner  
Prize share: 1/3



H. Robert Horvitz  
Prize share: 1/3



John E. Sulston  
Prize share: 1/3

The Nobel Prize in Physiology or Medicine 2002 was awarded jointly to Sydney Brenner, H. Robert Horvitz and John E. Sulston *"for their discoveries concerning genetic regulation of organ development and programmed cell death"*.

Photos: Copyright © The Nobel Foundation

# 發育生物學的發展史

**描述性的胚胎學** – 以顯微鏡觀察來描述各種動物的發育過程

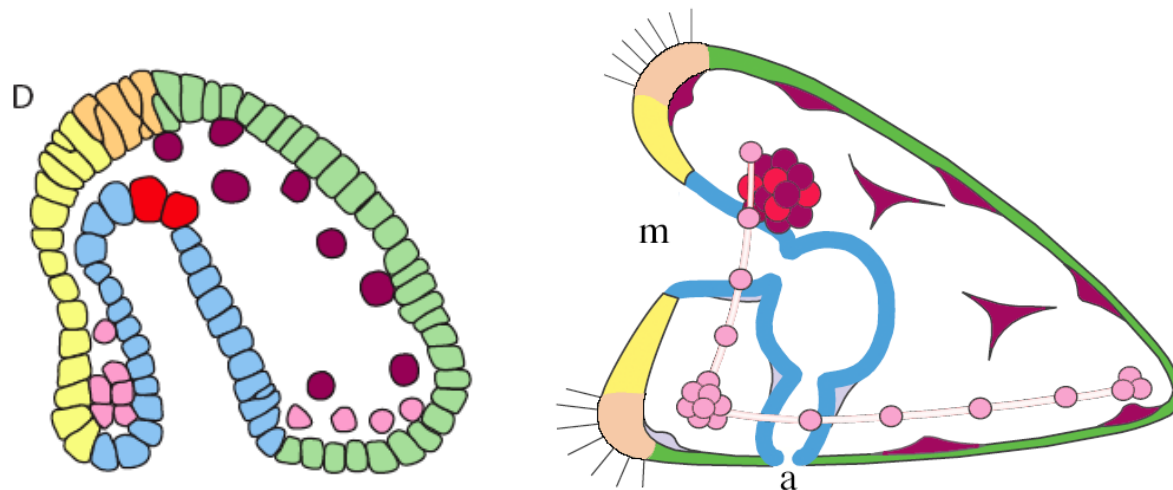
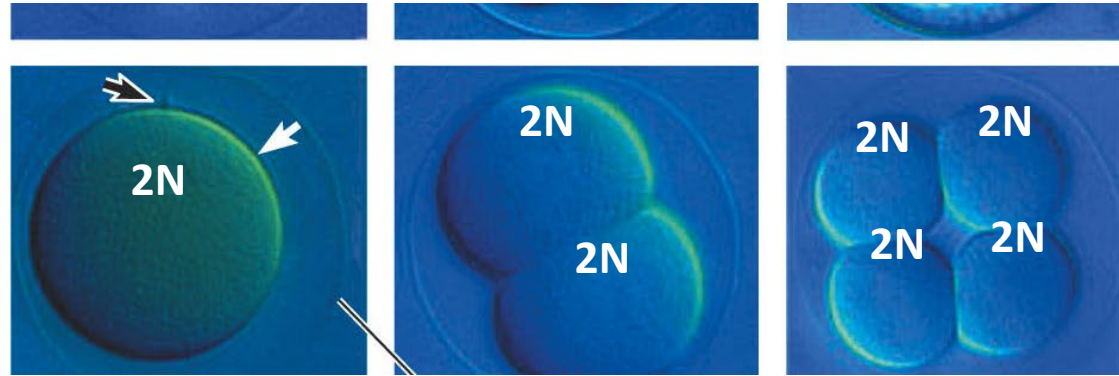
**實驗胚胎學** – 二十世紀初胚胎學家利用顯微手術操弄胚胎 (主要是用蛙胚和海膽胚胎) 以了解胚胎發育的機制

**發育遺傳學** – 利用突變的果蠅來篩選與發育相關的性狀

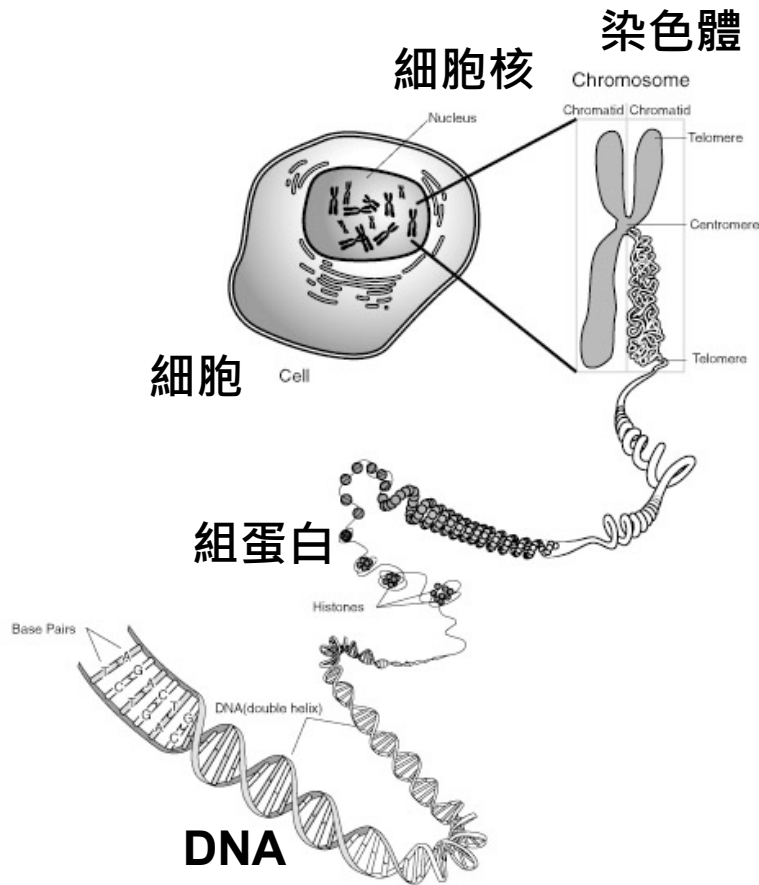
**現代發育生物學** – 奠基於描述性胚胎學，結合實驗胚胎學、發育遺傳學、與分子生物學的技术與知識來瞭解發育的分子機制

現代發育生物學的研究課題：  
胚胎的每一個細胞都含有相同的基因，胚胎如何發育成複雜的個體？  
怎麼知道在哪裡進行原腸化？如何決定體軸？  
如何產生不同的胚層、細胞種類、器官？

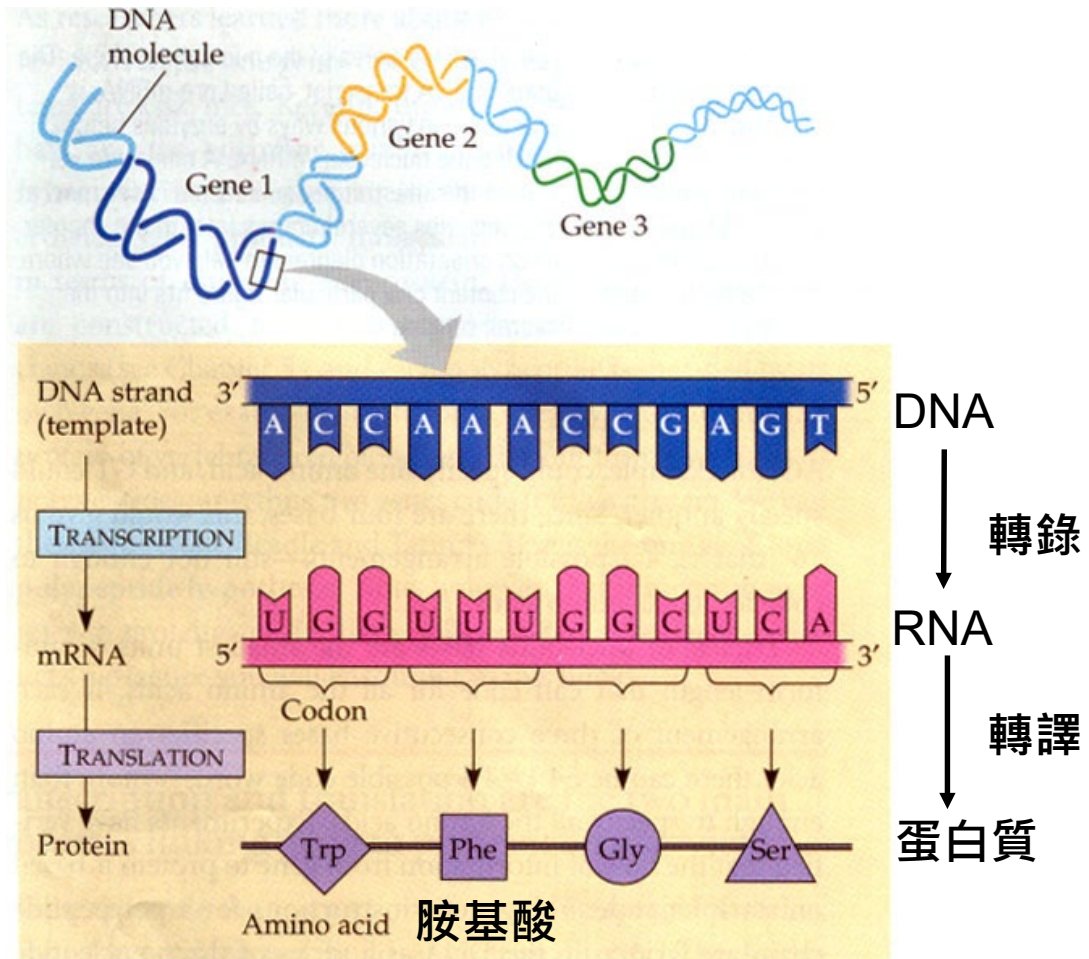
精、卵 (單套染色體N)  
↓  
受精 (雙套染色體2N)  
↓  
卵裂 (雙套染色體2N)



# 基因(Gene)- 遺傳的基本單位, 由片段的DNA組成

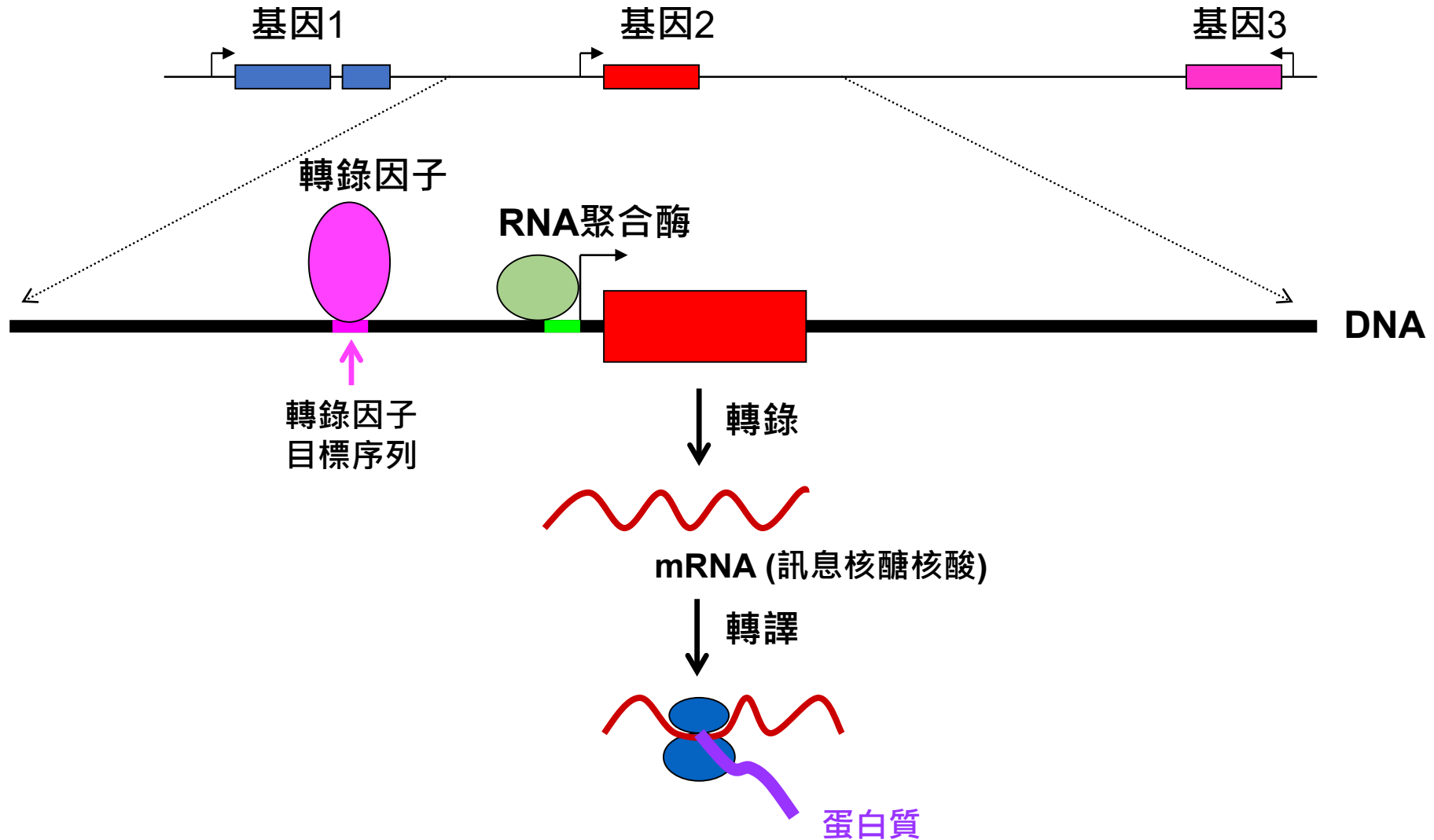


(National Genome Research Institute, USA)



(Campbell, *Biology*)

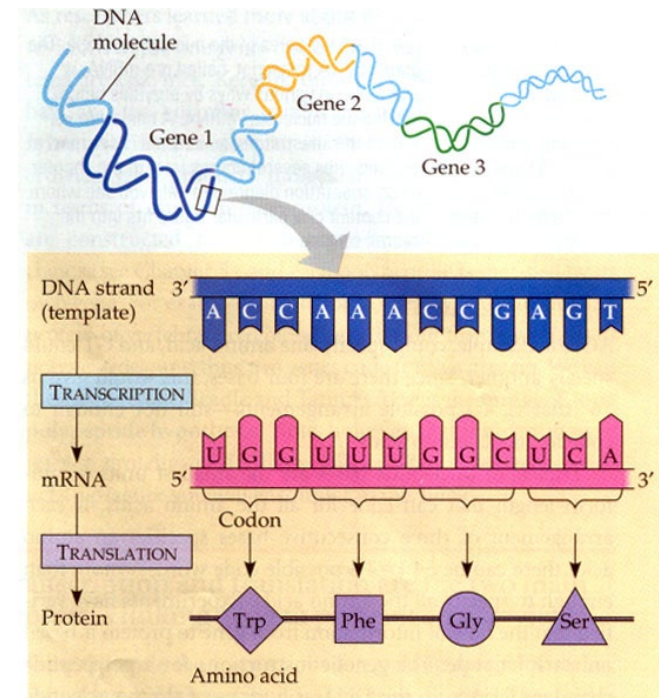
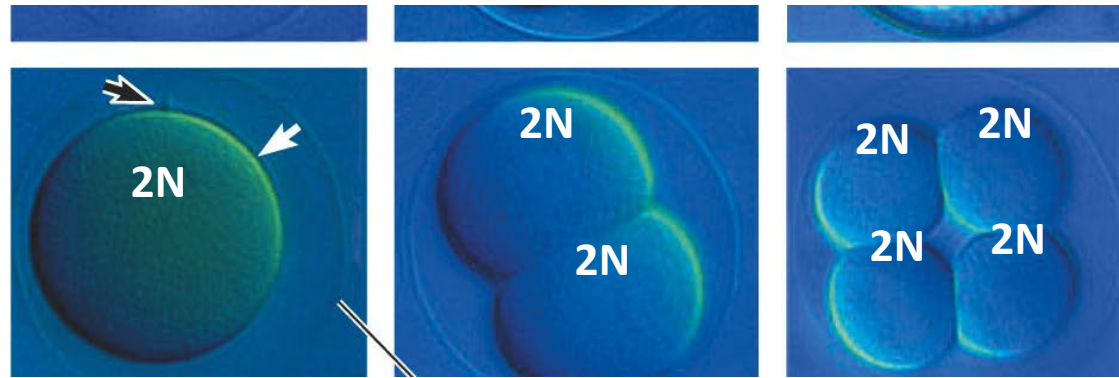
# 基因調控-基因轉錄的開啟與關閉





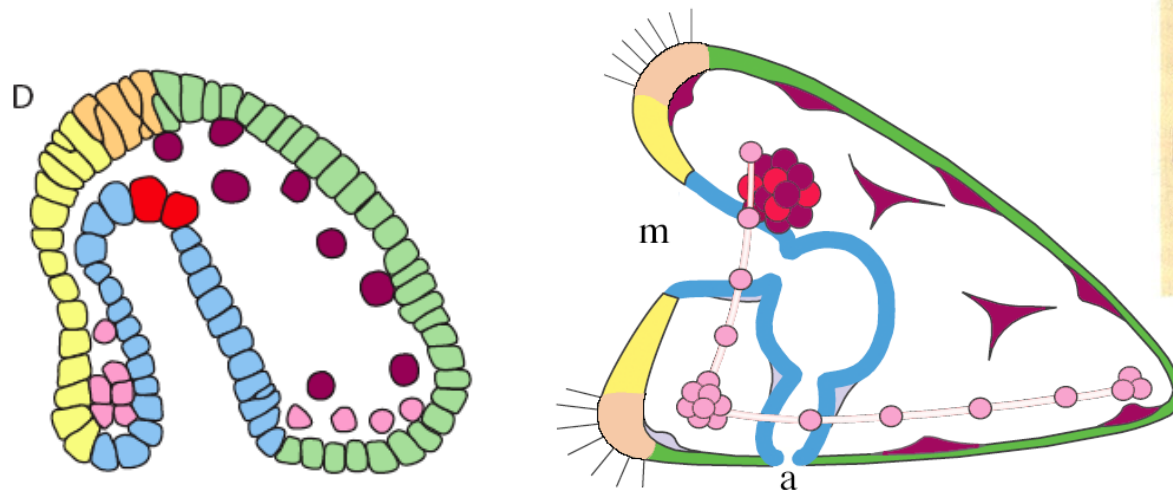
現代發育生物學的研究課題：  
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精、卵 (單套染色體N)  
 ↓  
 受精 (雙套染色體2N)  
 ↓  
 卵裂 (雙套染色體2N)



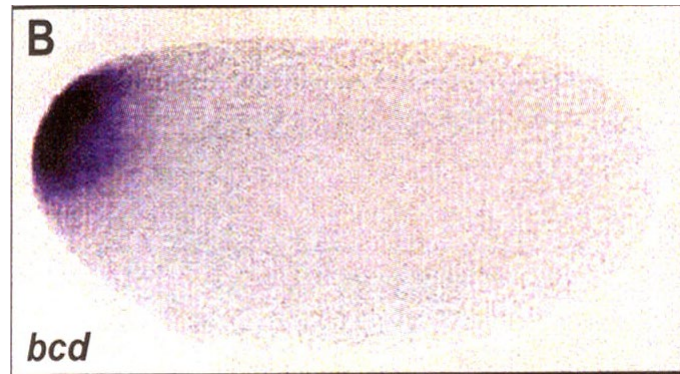
在胚胎發育的過程中，基因如何被調控？

特定基因如何在特定的時空被開啟或關閉？

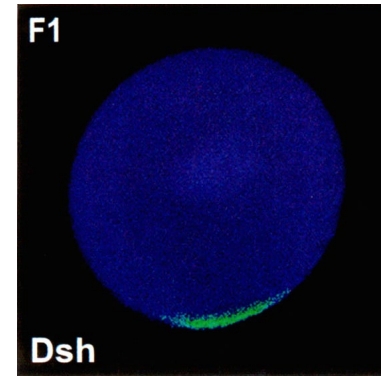


# 某些RNA或蛋白質在未受精卵或受精卵內就呈現不平均的分佈

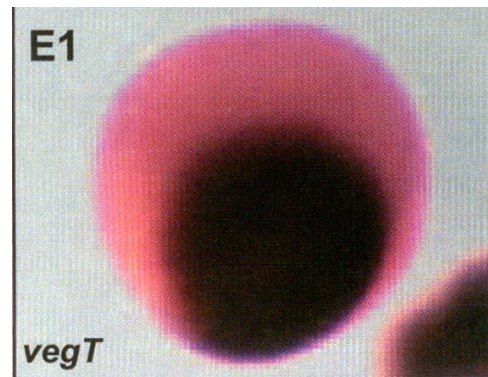
果蠅卵



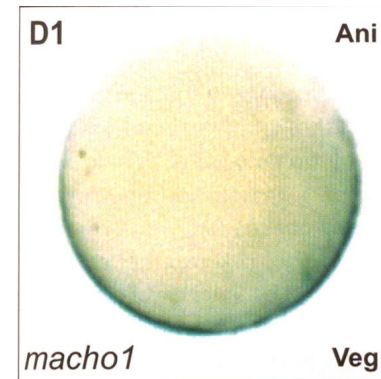
海膽卵



爪蟾卵



海鞘卵

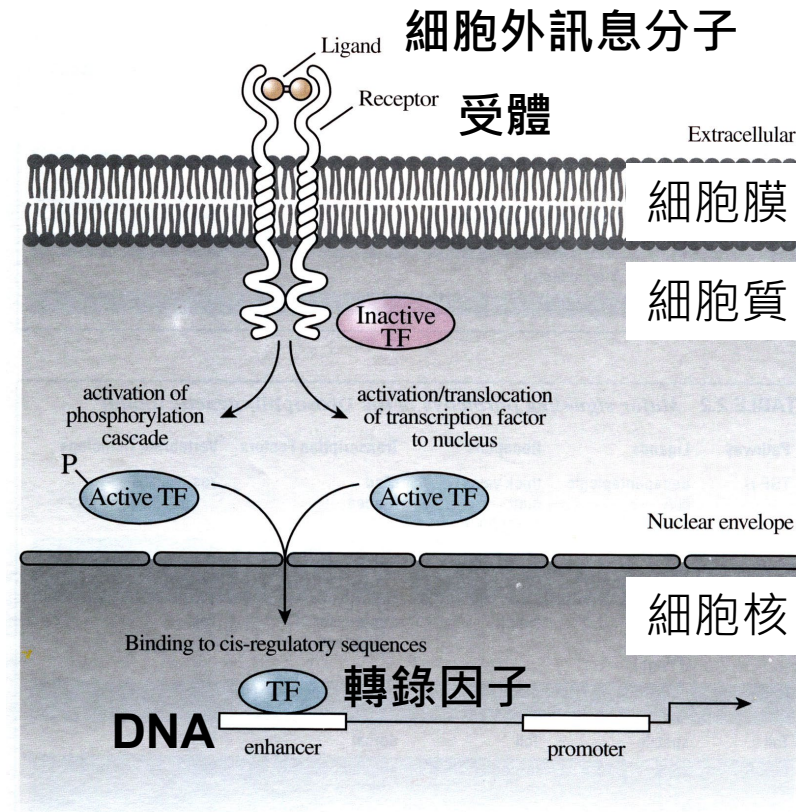
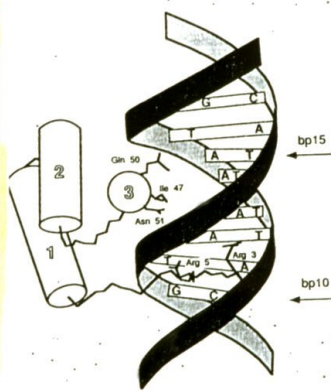
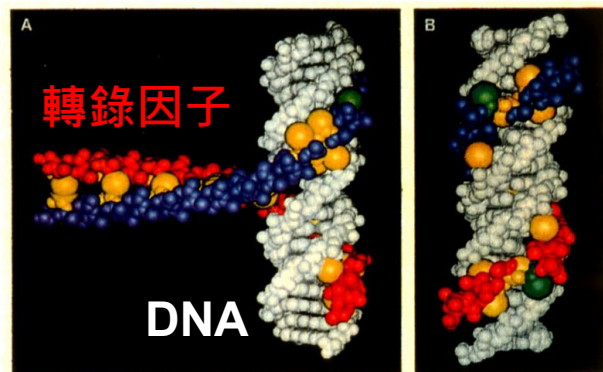


# 這些不均勻分布的分子通常為”工具分子”，能影響基因表現 (轉錄開啟或關閉)

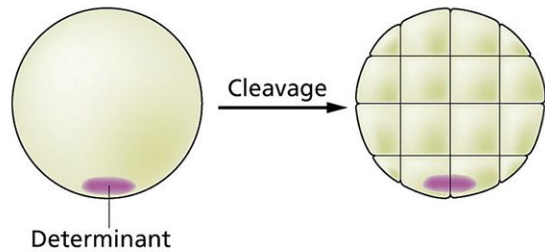


工具分子包括：

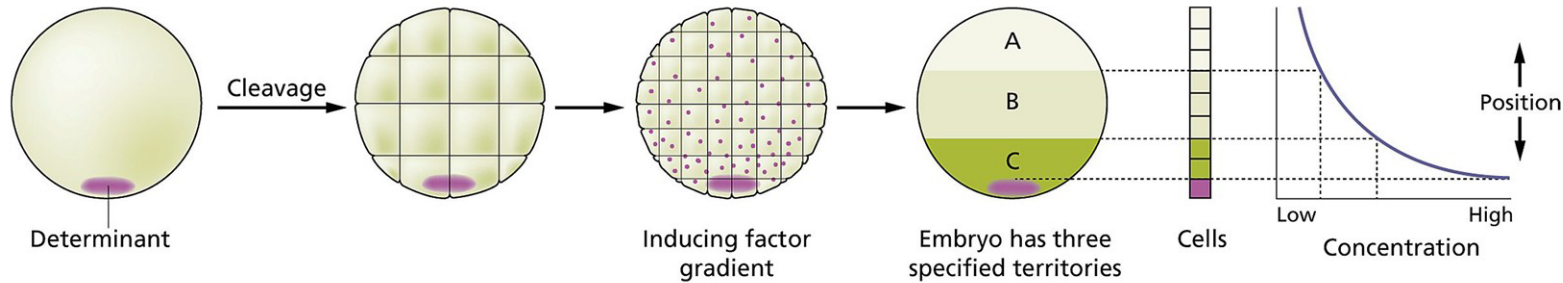
1. **轉錄因子**：在細胞核內會與DNA結合，調控基因表現
2. **訊息分子**：會分泌到細胞外經由訊息傳遞至細胞內影響轉錄因子的活性



在受精卵內分佈不均的轉錄因子或訊息分子，在早期卵裂過程中，只有部分細胞含有這些工具分子，因此基因在胚胎的不同部位有不同的調控方式



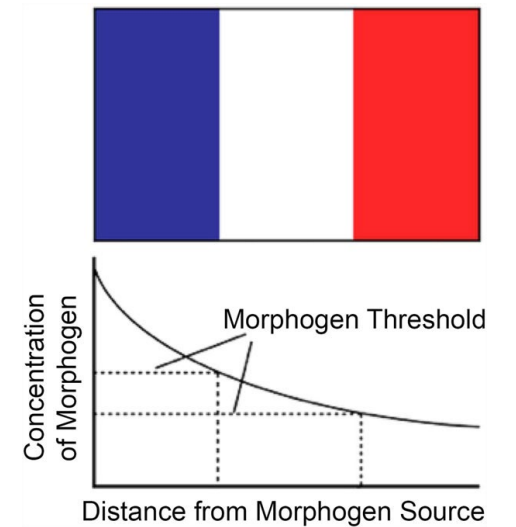
分佈不均的轉錄因子，僅在其存在細胞開啟下游基因



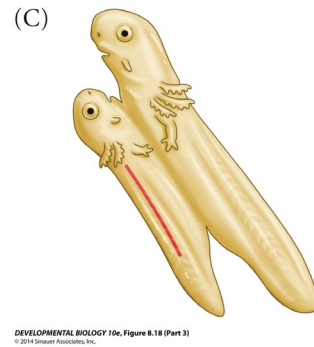
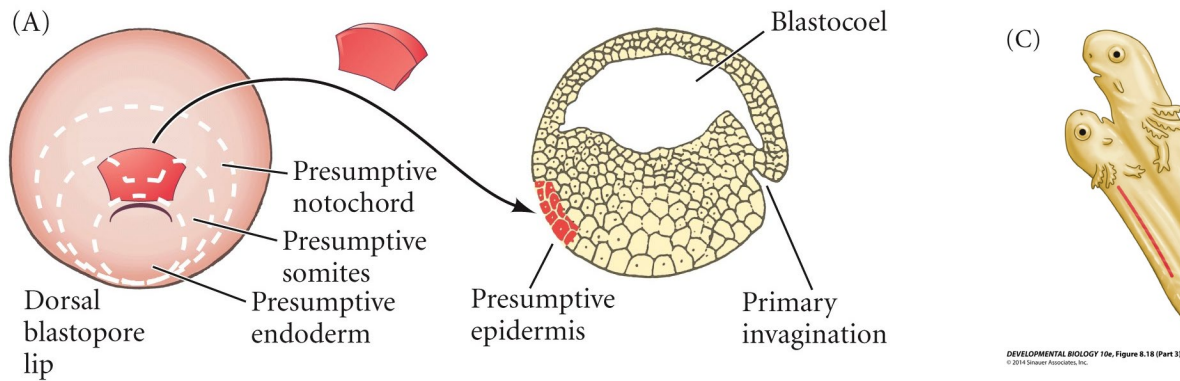
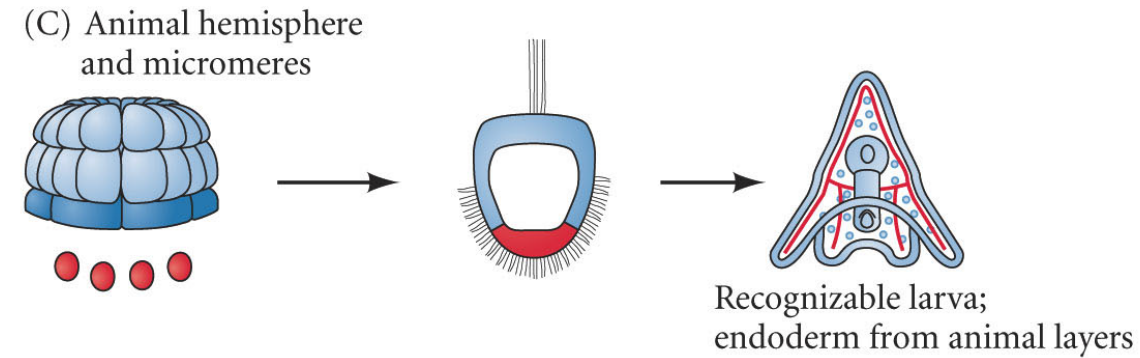
分佈不均的訊息分子，釋放出細胞外後形成濃度梯度，被其他細胞接收後，不同濃度會造成不同的反應

C區的細胞具有誘導B和A區細胞的能力

The French flag model



# 實驗胚胎學 – “剪下”與“貼上”的實驗



**誘導**：釋放出訊息分子，其他細胞接收後改變基因調控，影響細胞命運

**實驗結論：**

海膽胚胎的小細胞球具有**誘導**其他細胞改變命運的能力

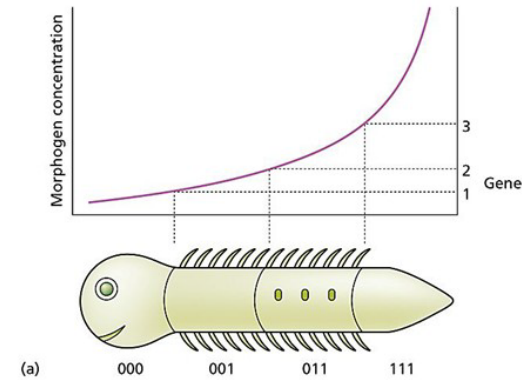
蝾螈胚胎胚口的背面細胞具有**誘導**其他細胞改變命運的能力

# 訊息分子的濃度梯度 Morphogen gradients

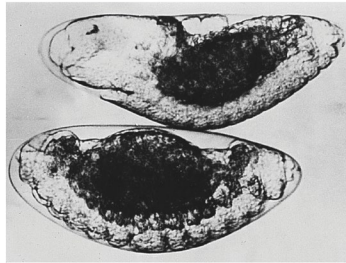
**Source:** the region that produces the morphogen

**Sink:** the region that destroys the morphogen

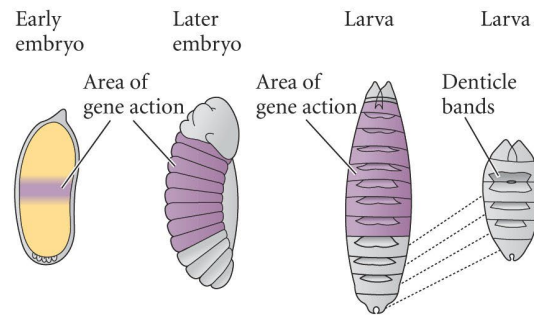
閾值反應 “threshold responses”



Gene on = 1  
Gene off = 0



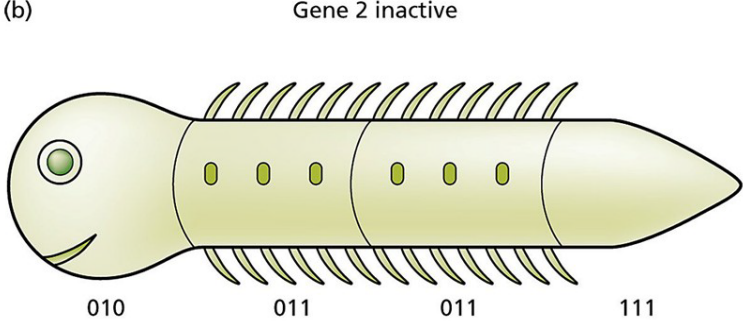
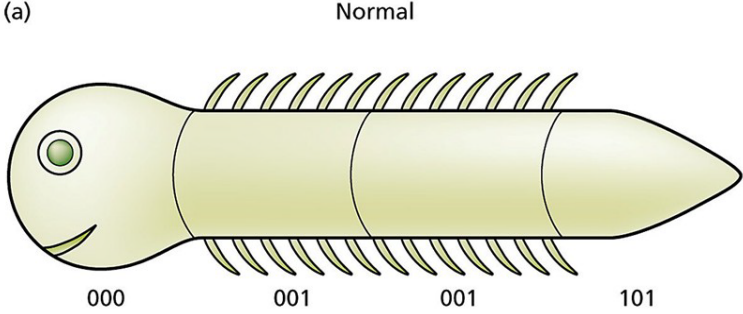
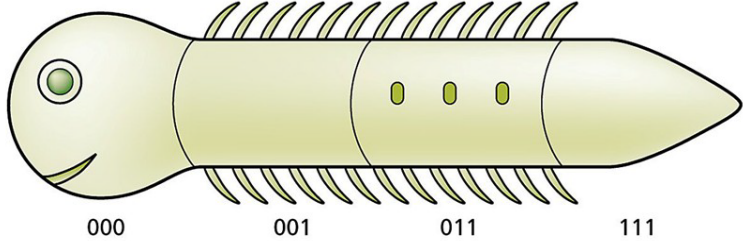
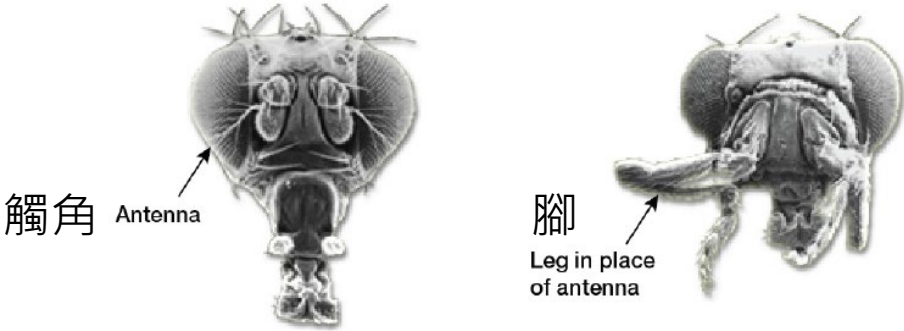
(A) Gap: *Krüppel*



# Homeotic mutations

(同源異形突變型)

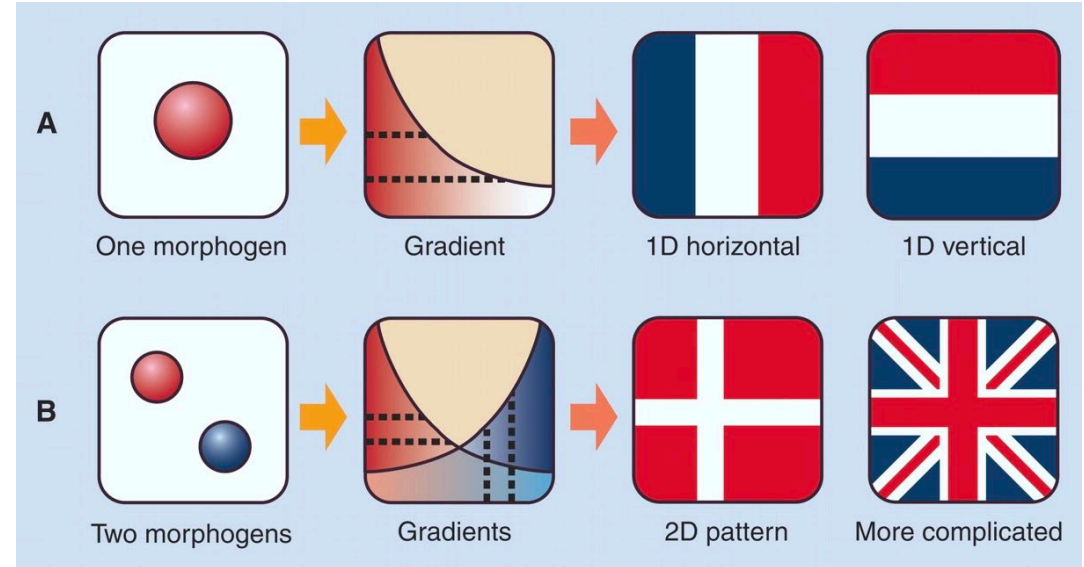
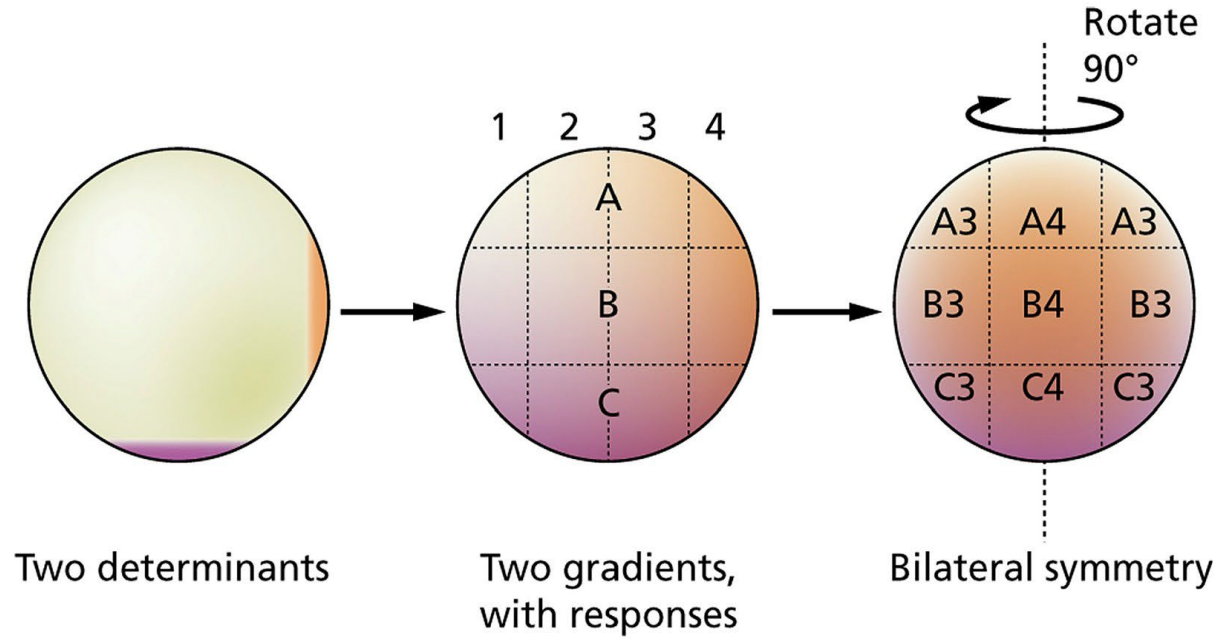
- convert one body part into another



*Essential Developmental Biology*, Third Edition. Jonathan M.W. Slack.  
© 2013 John Wiley & Sons, Ltd. Published 2013 by John Wiley & Sons, Ltd.

**Fig. 2.15** Homeotic mutants. (a) Normal genotype and phenotype. (b) Loss-of-function mutation of gene 2 causes second body segment to resemble the first. (c) Gain-of-function mutation of gene 2 causes first body segment to resemble the second. This example assumes that the abnormal codings (010 and 101) do not produce homeotic effects.

# 兩個不平均分佈的轉錄因子或訊息分子可將胚胎分成不同區塊



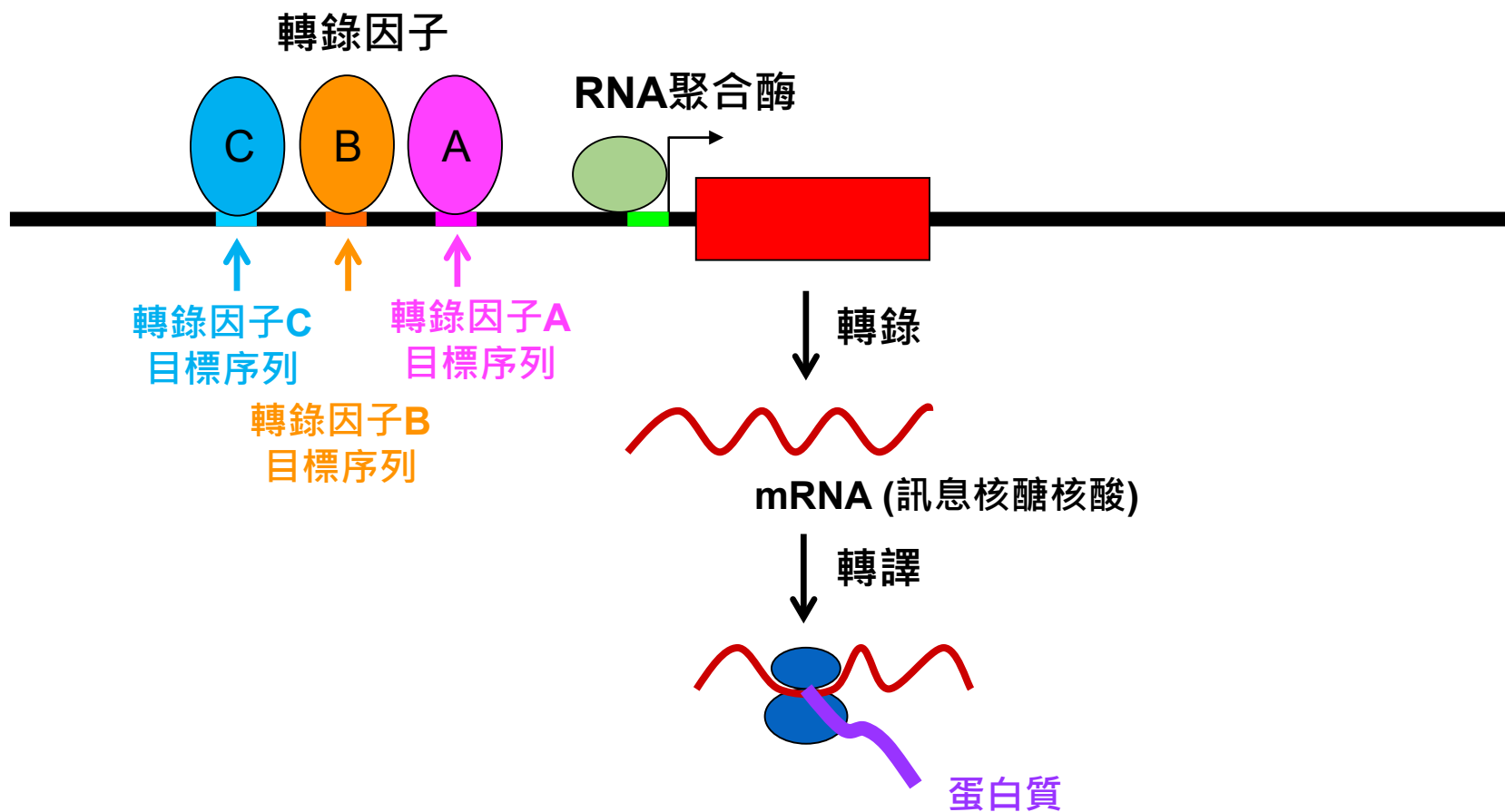
*Essential Developmental Biology*, Third Edition. Jonathan M.W. Slack.  
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**Fig. 2.2** Generation of bilateral symmetry with two determinants. Two gradients partition the embryo into territories along two axes. The resulting embryo has territories arranged symmetrically around a medial plane.



# 基因調控

一個基因的開啟與關閉可由數個轉錄因子調控

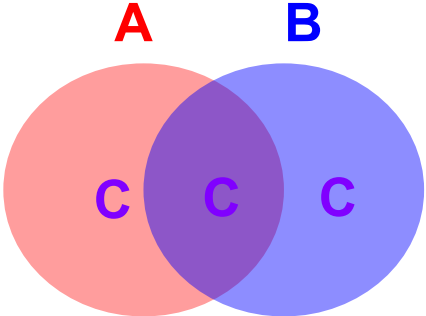
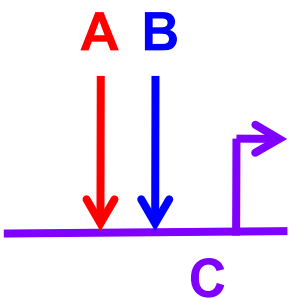


# 基因表現的調控邏輯

調控序列決定了轉錄因子的共同作用方式及基因的表現位置

- DNA序列影響基因開啟的時間與地點

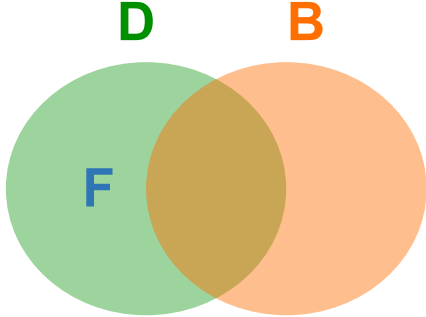
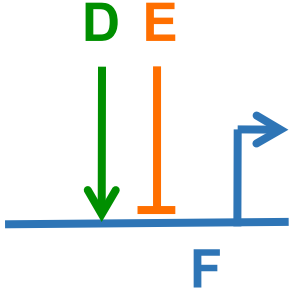
兩個  
促進表現的轉錄因子  
協同作用



C is on if  
(1) A and B  
(2) A or B

交集  
**VS.**  
聯集

促進表現的轉錄因子  
與  
抑制表現的轉錄因子  
協同作用

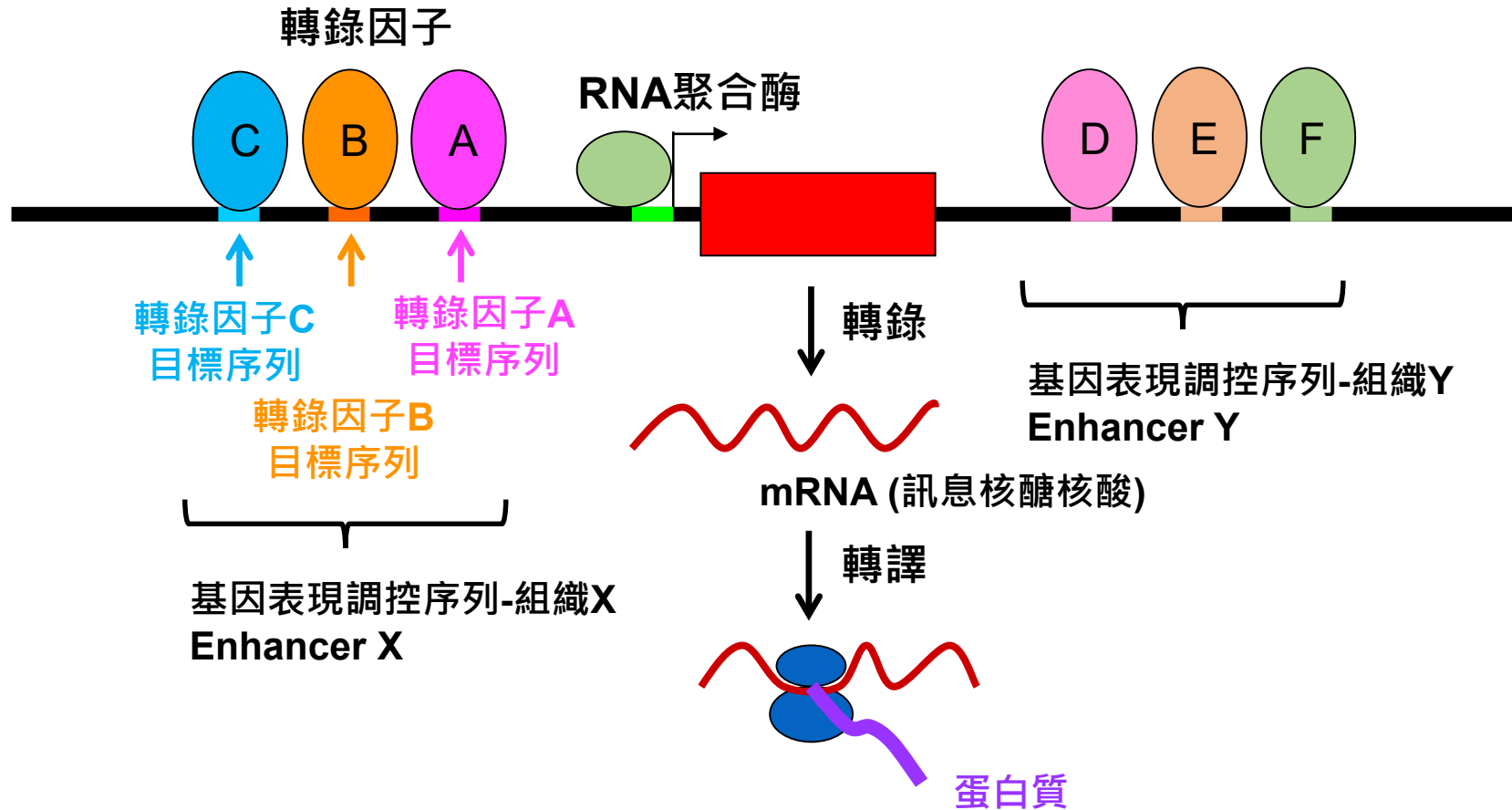


F is on if  
D but not E

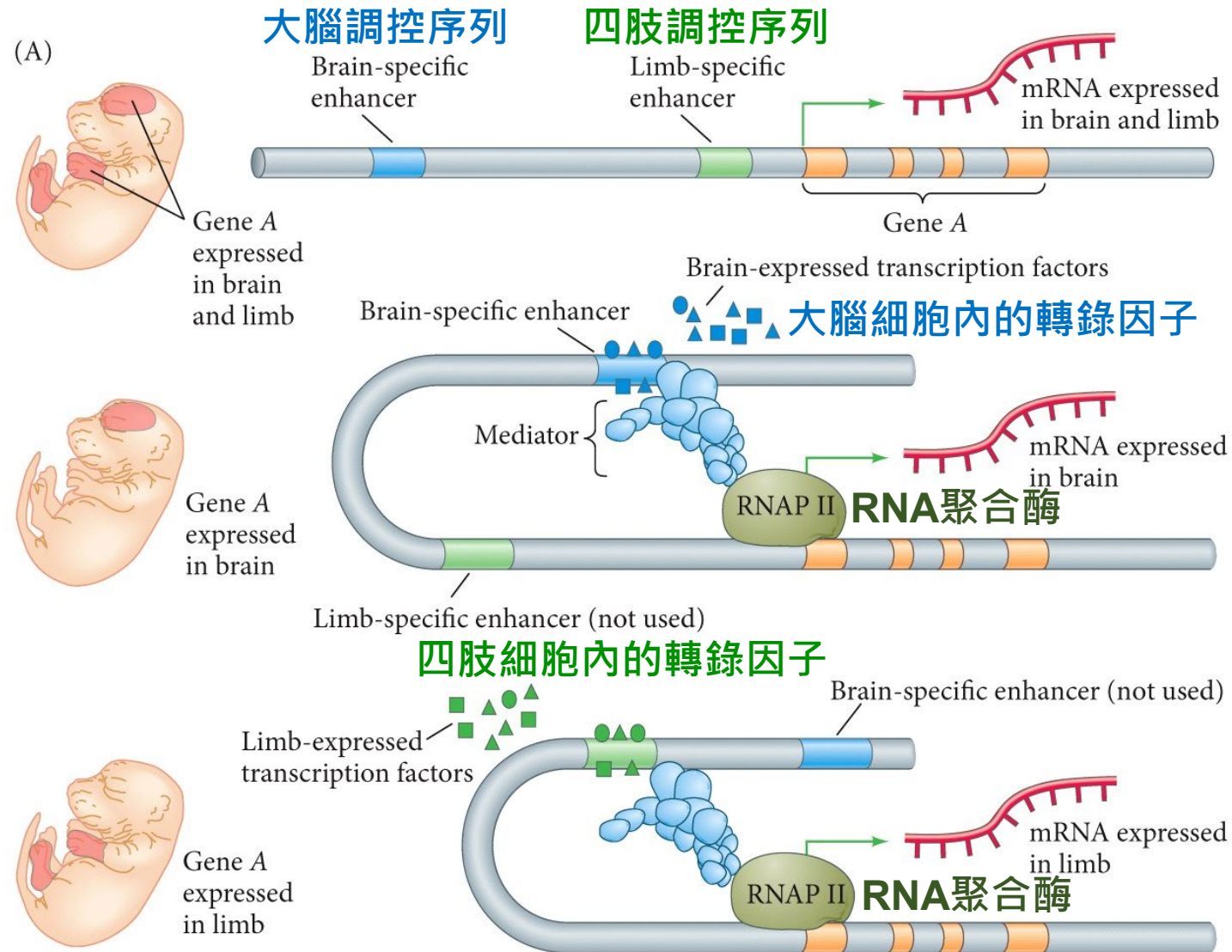
差集

# 基因調控

## 基因的開啟與關閉-時間與地點指令

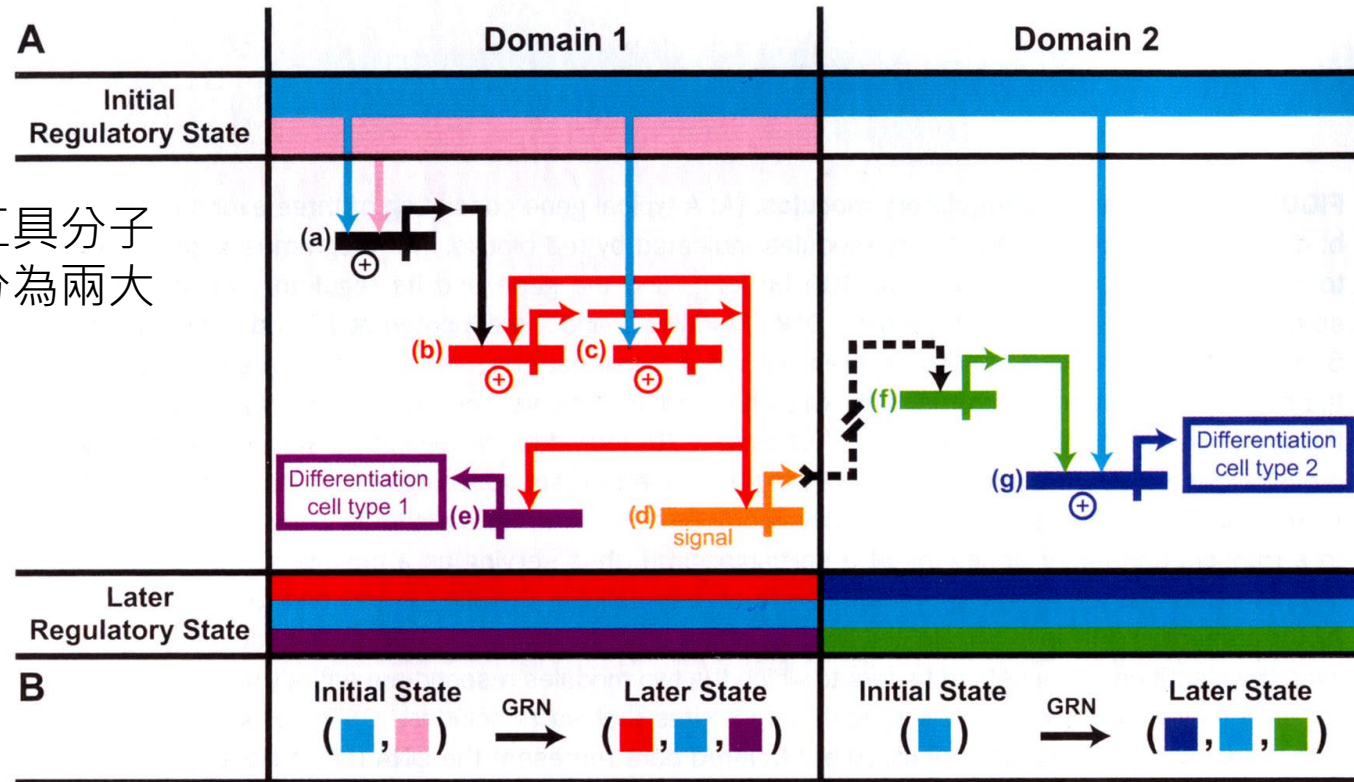


# 基因表現的模組化調控 – 組織特異性的表現調控



# 發育基因調控網路

假想的胚胎因為工具分子分佈不平均而區分為兩大區塊

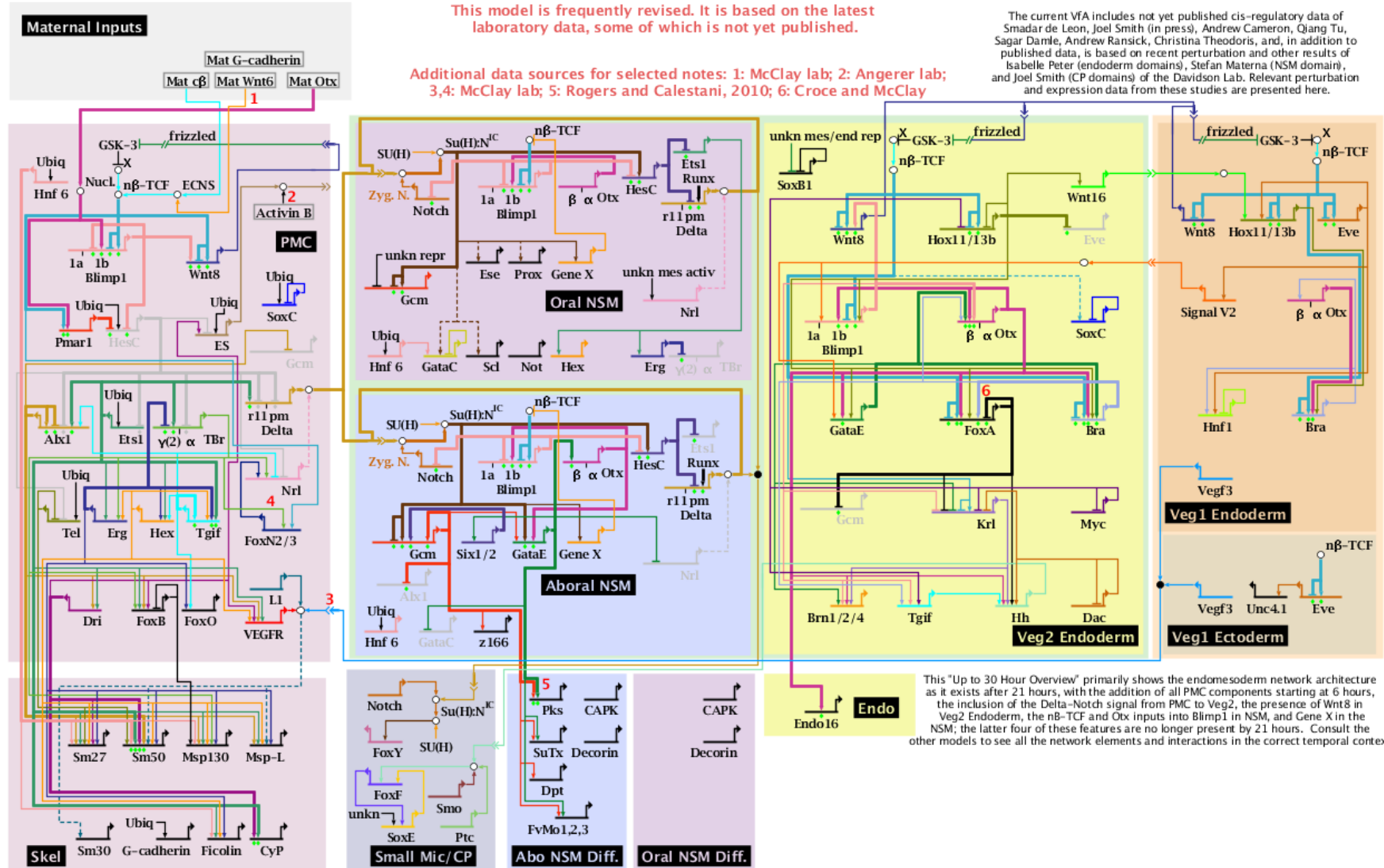
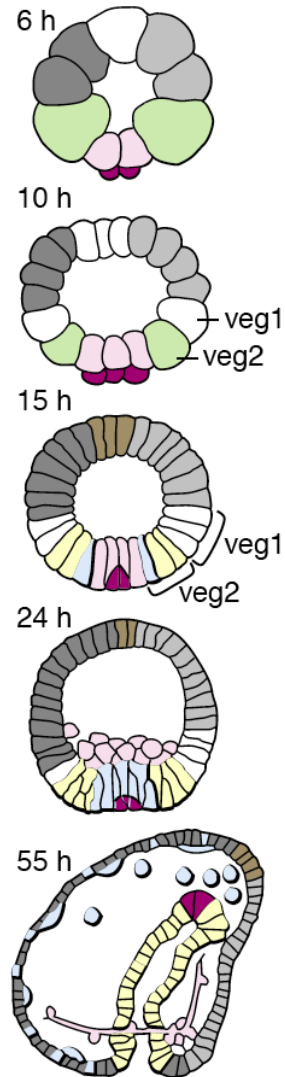


- 工具分子：轉錄因子與訊息分子
- 轉錄因子bc基因之間的正向回饋
- 訊息分子d由第一區輸出，提供訊息給第二區，得到訊息的第二區開啟基因f
- 隨著發育的進展，胚胎被區分為更多區塊，各自含有不同的轉錄因子組合，能夠開啟不同的基因
- 訊息分子能夠影響周邊細胞的狀態（誘導）

# 海膽胚胎的中內胚層發育基因調控網路

Endomesoderm Specification up to 30 Hours

November 21, 2011



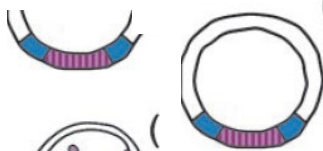
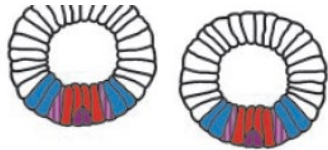
Copyright © 2001-2011 Hamid Bolouri and Eric Davidson

# 中內胚層發育基因調控網路的主要迴路



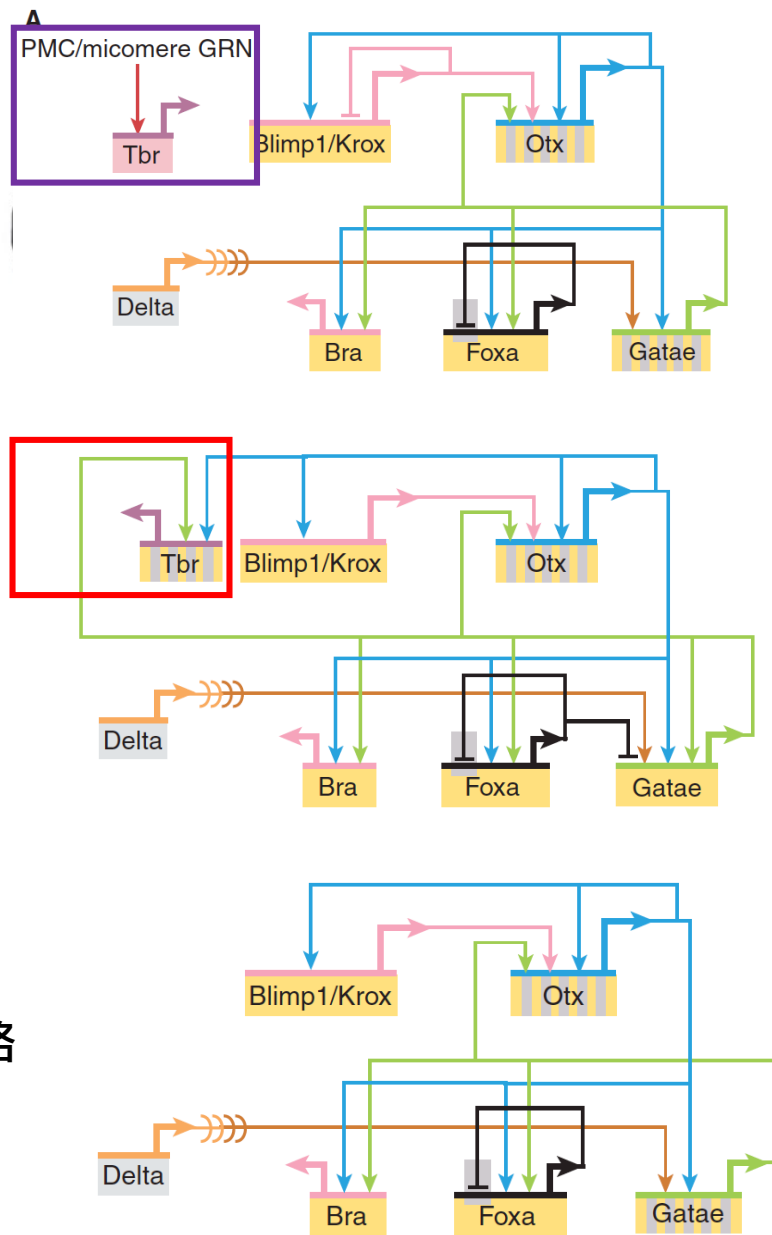
?

生活在五億年前海膽與海星  
的共同祖先



發育 & 演化

海膽與海星共有的迴路



## 發育生物學 (Developmental Biology)

研究物種的發育基因調控網路，以了解單細胞受精卵如何發育成複雜的多細胞個體

## 演化與發育生物學 (Evolutionary Developmental Biology, EvoDevo)

透過比較現生動物的發育基因調控網路，以推測祖先的發育基因調控網路，並探討在演化過程中DNA發生何種改變，使發育機制改變並導致型態的變異



# 中研院細生所蘇怡璇老師實驗室

- 研究海洋無脊椎棘皮動物海膽與半索動物玉柱蟲的發育機制，以探討後口動物的演化與脊索動物特徵的起源

