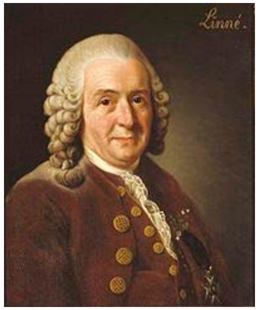
動物的發育機制與演化

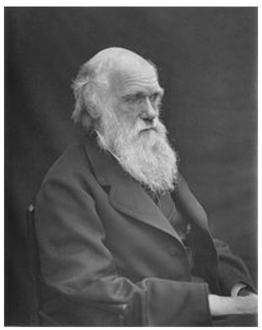
中央研究院
細胞與個體生物學研究所
蘇怡璇

2015. 5. 9.

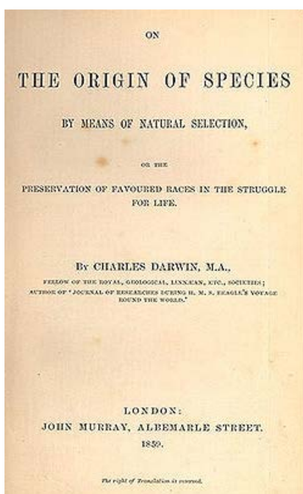
動物的分類與演化



林奈 (1707-1778) 瑞典生物學家
建立現代生物命名法二名法的基礎
例如: 人 (智人 *Homo sapiens*)，黑腹果蠅 (*Drosophila melanogaster*)



達爾文 (1809-1882) 英國生物學家
提出“共同祖先”的概念，認爲現生生物是由共同祖先發生變異，變異傳至後代，經由天擇演化而來


ON

THE ORIGIN OF SPECIES

BY MEANS OF NATURAL SELECTION,

OR THE

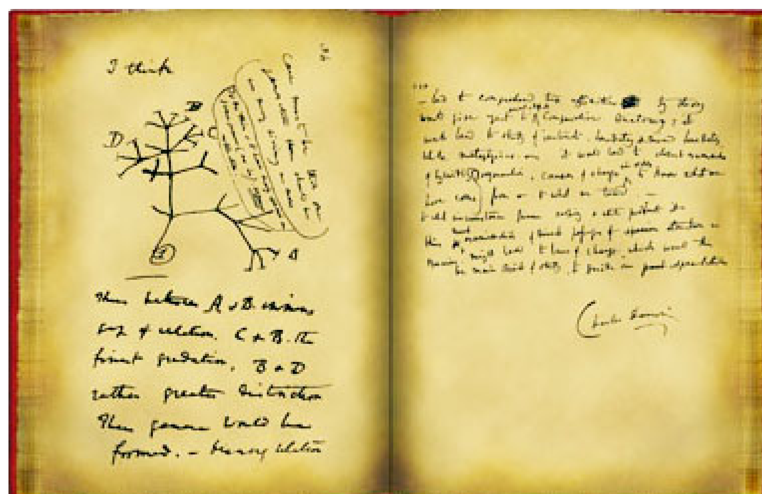
PRESERVATION OF FAVOURED RACES IN THE STRUGGLE FOR LIFE.

By CHARLES DARWIN, M.A.,

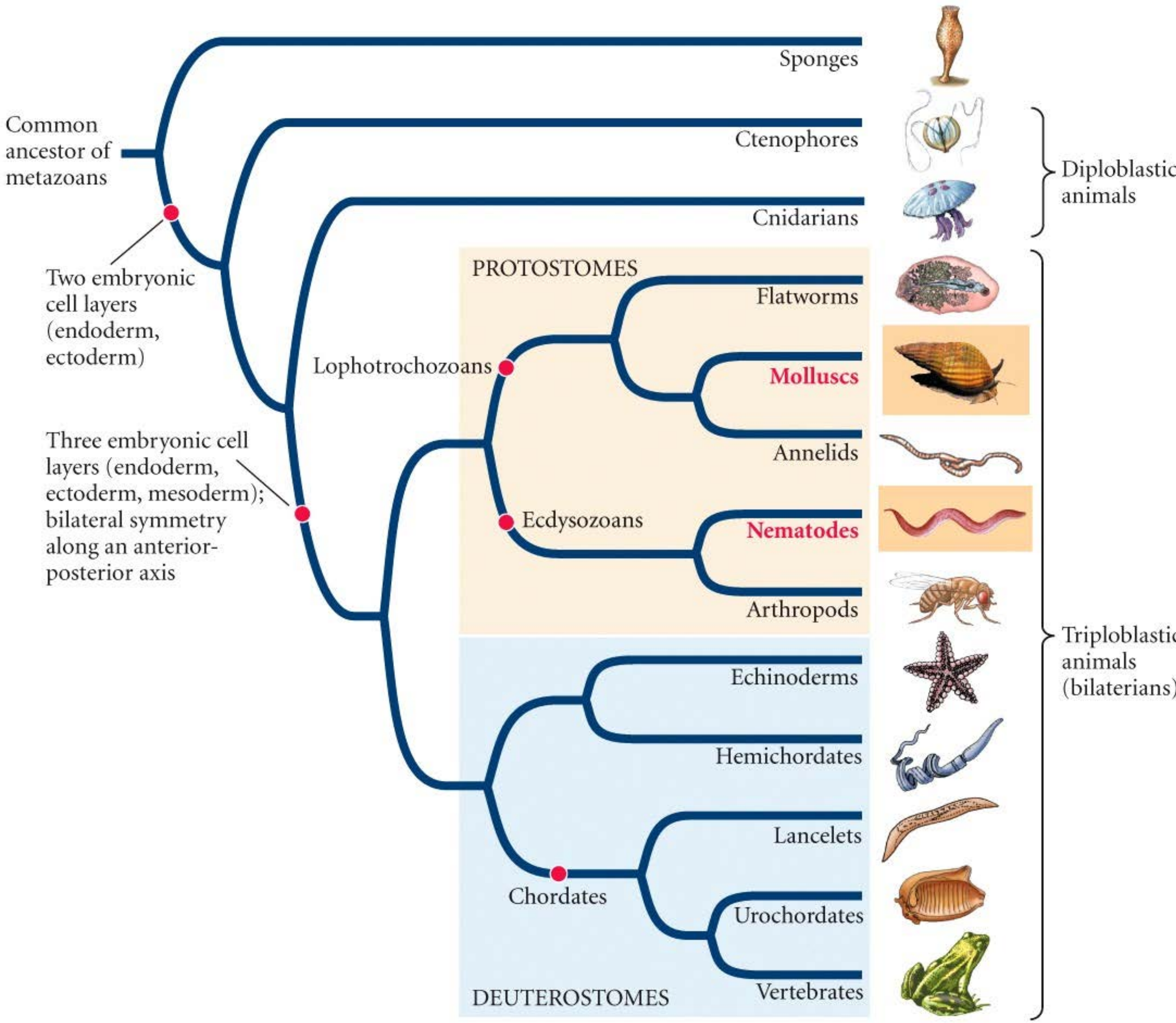
FELLOW OF THE ROYAL, GEOLOGICAL, LINNÆAN, ETC., SOCIETIES;
AUTHOR OF 'JOURNAL OF RESEARCHES DURING H. M. S. BEAGLE'S VOYAGE ROUND THE WORLD.'

LONDON:
JOHN MURRAY, ALBEMARLE STREET.
1859.

The right of Translation is reserved.



35-40個動物門的親緣關係 (經由分子證據而來)

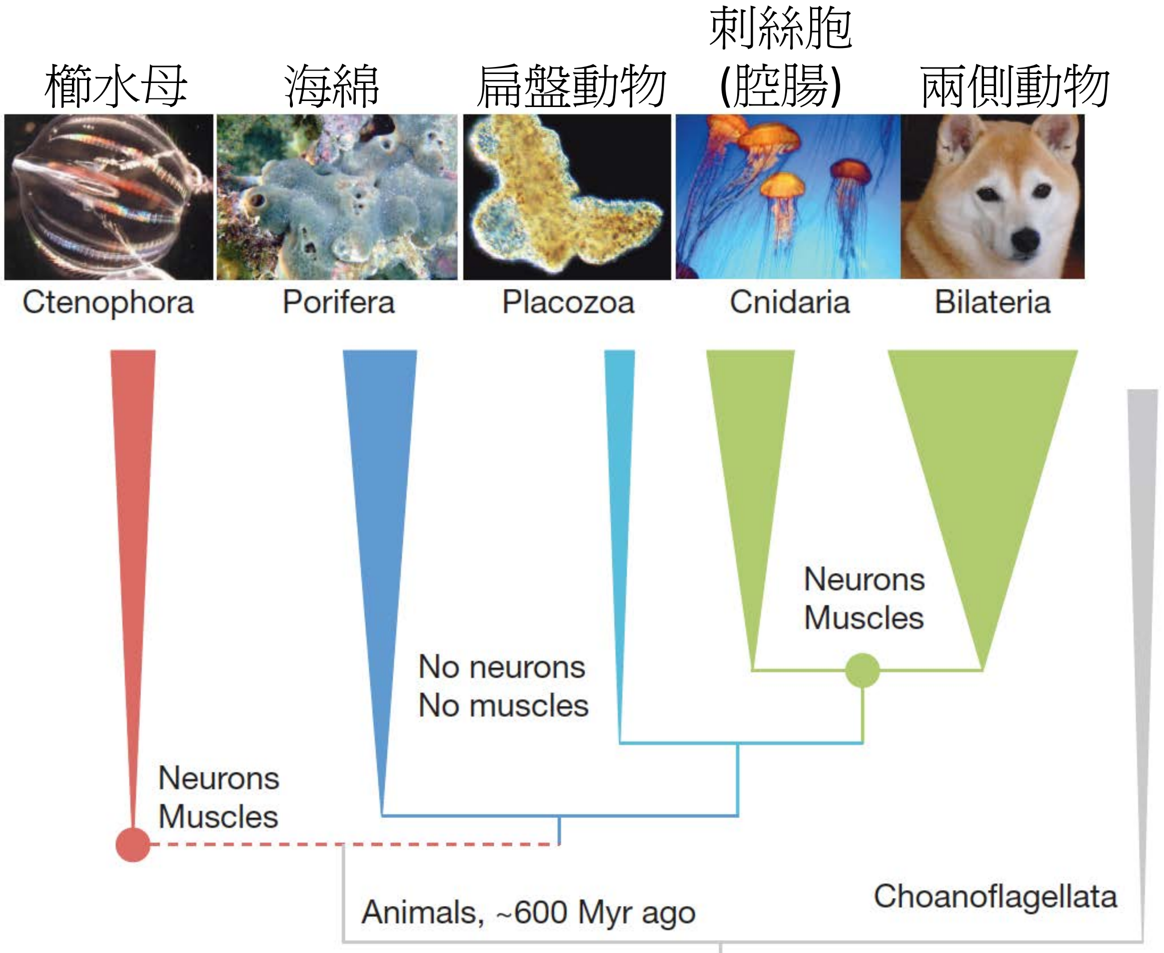


非兩側對稱動物

兩側對稱動物

***DEVELOPMENTAL BIOLOGY 10e*, Figure 5.1**

動物門的親緣關係還在持續解析中 (經由基因體及其他證據)

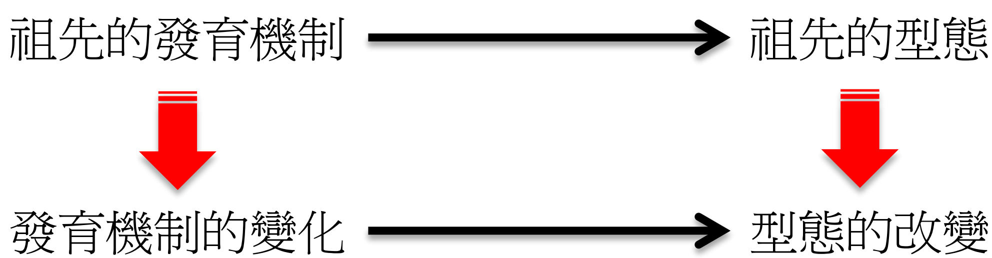


Moroz et al., 2014, Nature

每個動物門(綱、目、科、屬、種)都有其特殊的特徵和型態，這些特殊的特徵和型態是經由發育的過程而來。

例如：脊索動物門有脊索、脊椎動物亞門有脊椎、哺乳綱有毛髮並可哺乳、靈長目眼睛在臉的前面並有發達的大腦...

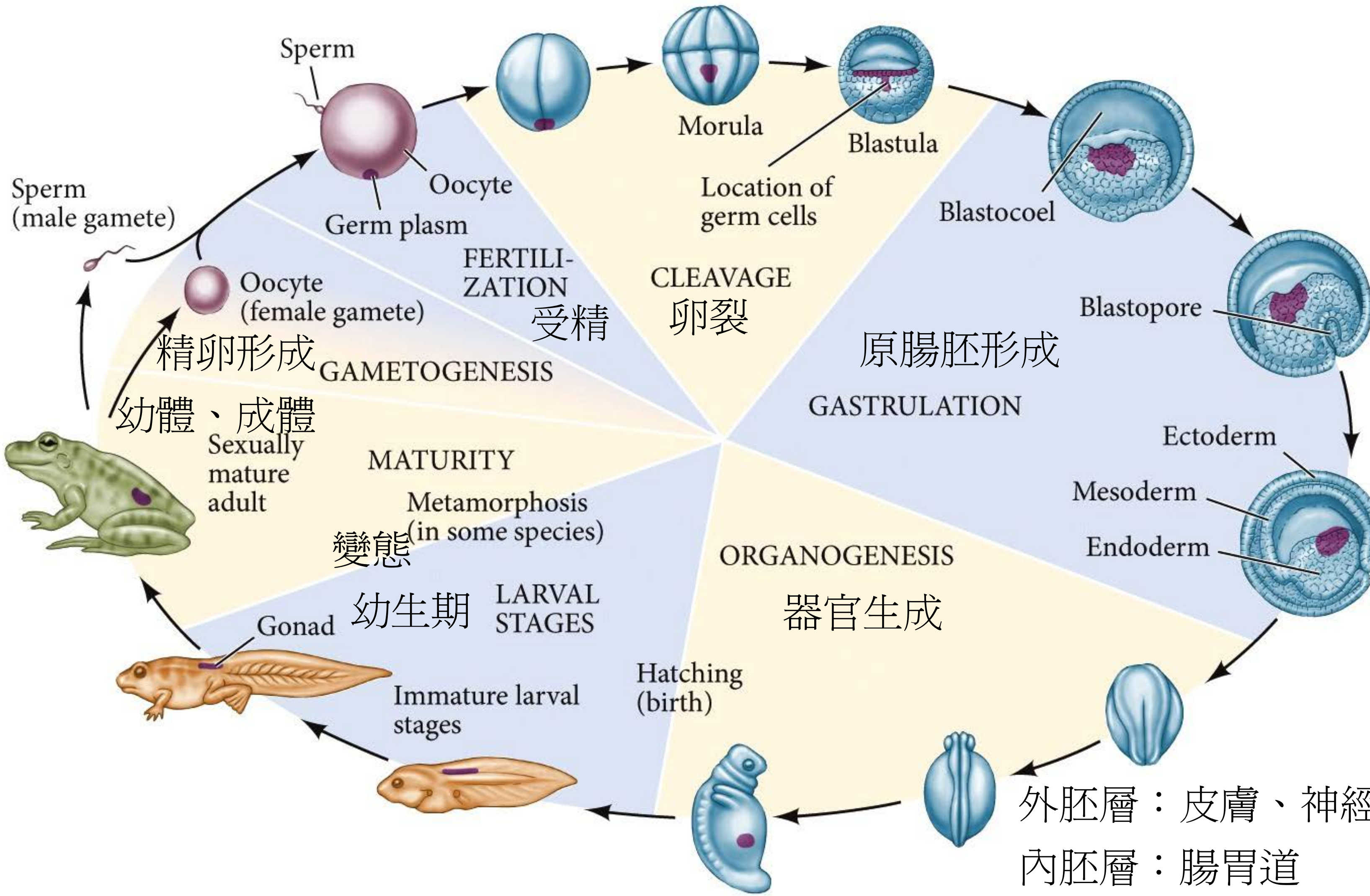
這些特殊的特徵和型態是如何演化出來的？



演化發育生物學 (Evolutionary Developmental Biology, EvoDevo)：
結合演化生物學與發育生物學，從發育機制的角度來探討演化的問題

動物的發育 （發育生物學研究的範疇）

- 生命的週期，由單細胞至多細胞個體的過程



外胚層：皮膚、神經

內胚層：腸胃道

中胚層：血球、肌肉、骨頭

DEVELOPMENTAL BIOLOGY 10e, Figure 1.1

早期胚胎發育過程

受精

精卵結合產生新個體，其基因組由父母而來

↓

卵裂

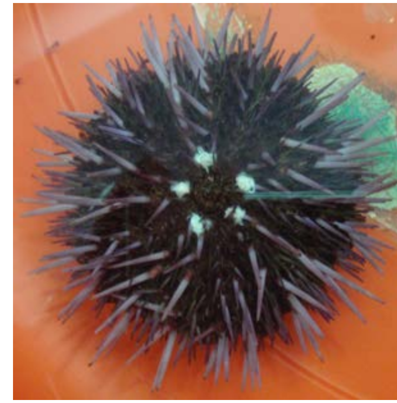
↓

原腸胚形成

↓

器官形成

公海膽



母海膽

海膽的受精

早期胚胎發育過程

受精

精卵結合產生新個體，其基因組由父母而來

↓

卵裂

快速的細胞分裂將受精卵分割成許多小細胞，形成囊胚

↓

原腸胚形成

↓

器官形成

海膽的卵裂

早期胚胎發育過程

海膽的卵裂

受精　精卵結合產生新個體，其基因組由父母而來

↓

卵裂　快速的細胞分裂將受精卵分割成許多小細胞，形成囊胚

↓

原腸胚形成

↓

器官形成

早期胚胎發育過程

受精

精卵結合產生新個體，其基因組由父母而來

↓

卵裂

快速的細胞分裂將受精卵分割成許多小細胞，形成囊胚

↓

原腸胚形成

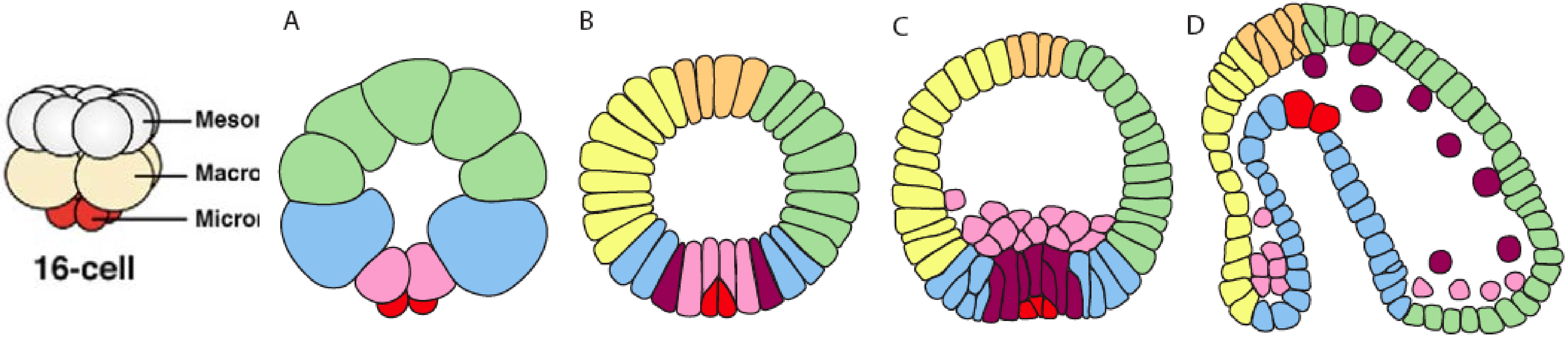
在原腸胚形成過程中，細胞開始移動，有新的位置和鄰居，形成不同的胚層 (外胚層、內胚層、中胚層)

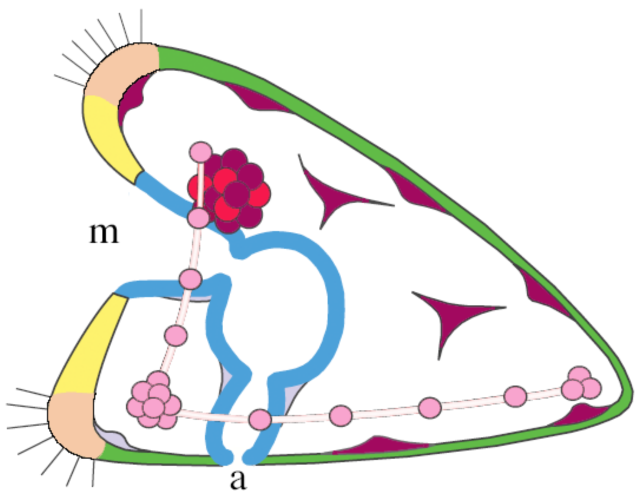
↓

器官形成

海膽的原腸胚形成

海膽的早期發育





- 口面外胚層
- 反口面外胚層
- 纖毛帶

} 外胚層

- 內胚層

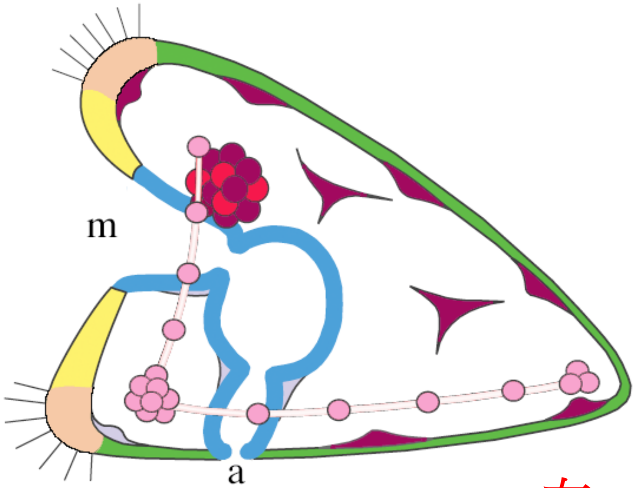
} 內胚層

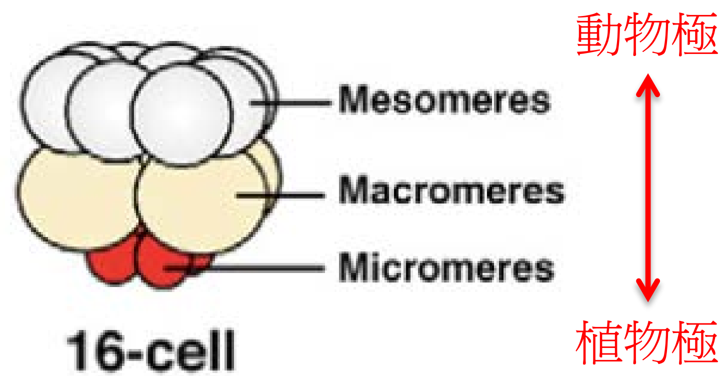
- 骨骼中胚層
- 植物板中胚層
- 先驅生殖細胞

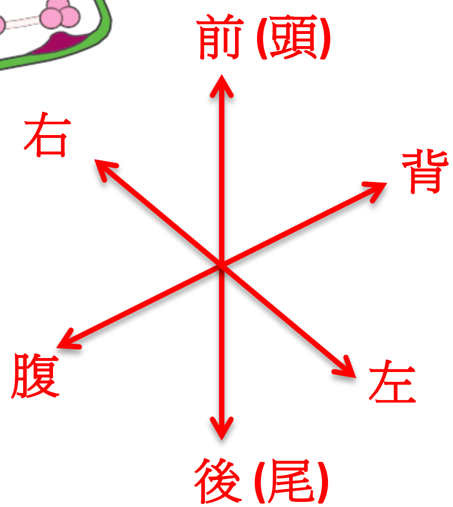
} 中胚層

- 骨針

身體的體軸與胚胎(或卵)的極性





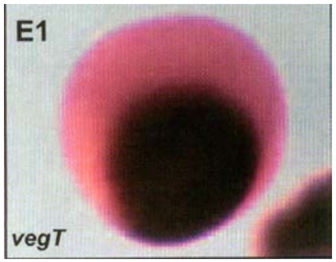


蛙卵- 深色爲動物極，淺色爲植物極

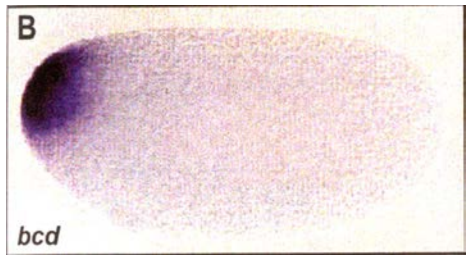
一開始如何建立極性？

1. 內部因素：在卵成熟的過程中，RNA或蛋白質在卵內就有不均勻的分佈

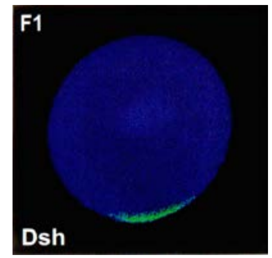
爪蟾卵



果蠅卵

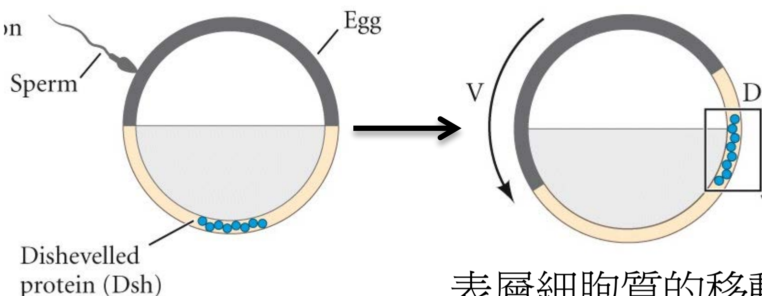


海膽卵



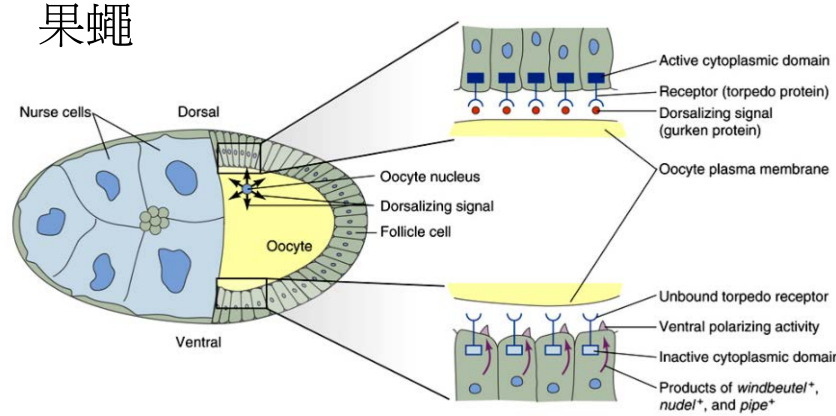
2. 外部因素：因爲精子進入的點或卵周圍局部的刺激

爪蟾



表層細胞質的移動

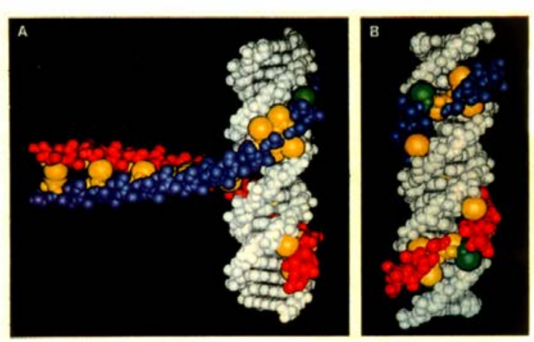
果蠅

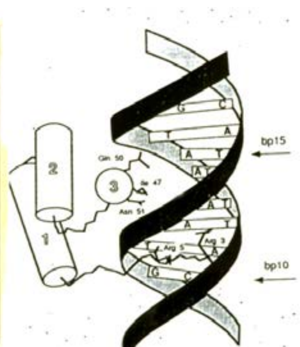


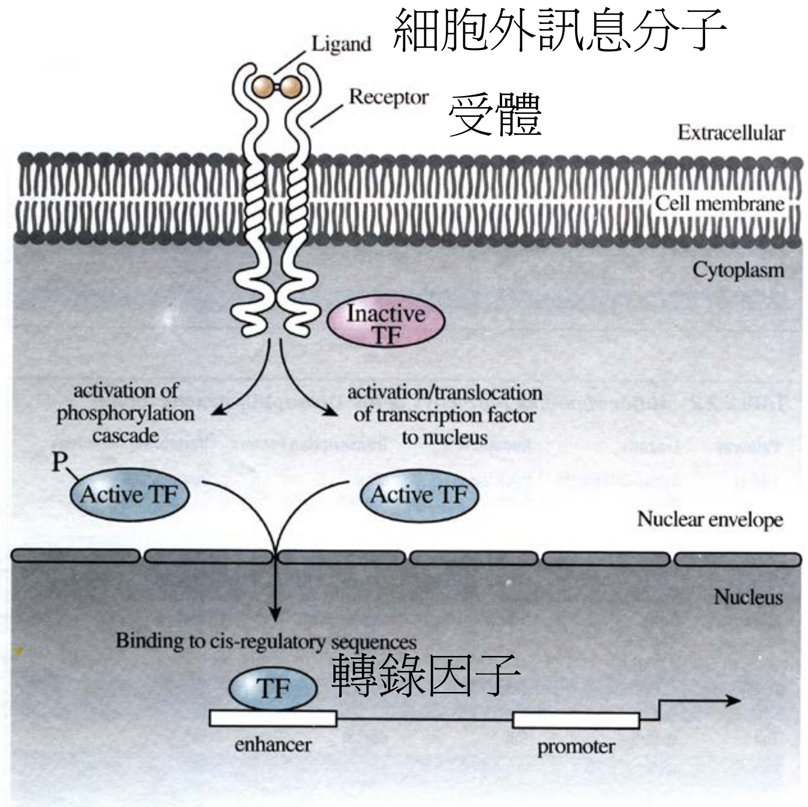
這些不均勻分布的分子通常為“工具分子”，能影響基因表現 (開啓或關閉)

工具分子包括：

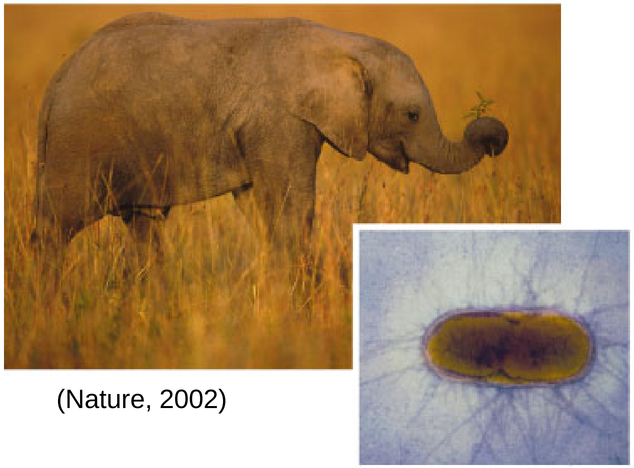
1. 轉錄因子：會與DNA結合，調控基因表現
2. 訊息傳遞分子：會影響轉錄因子的活性



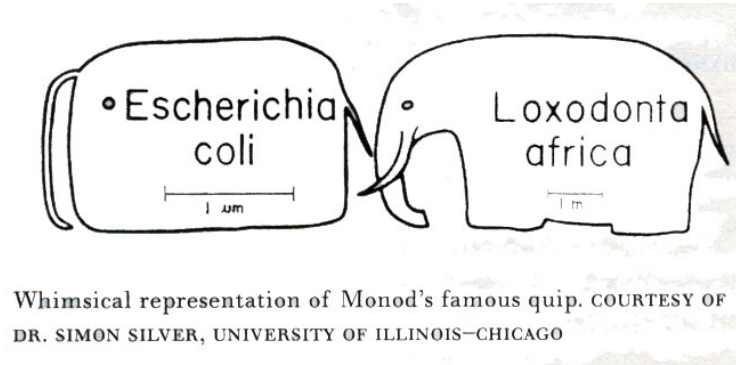




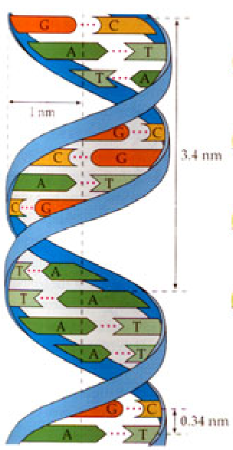
大腸桿菌與大象都有DNA



(Nature, 2002)

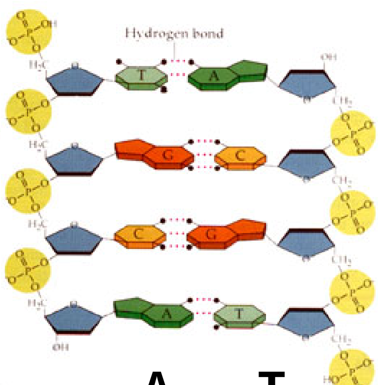


(Carroll, *Endless forms most beautiful*, 2005)



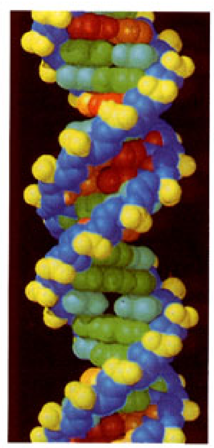
DNA雙股螺旋

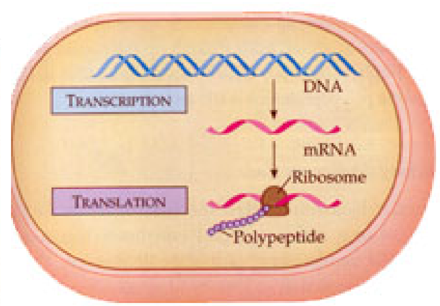
配對鹼基形成氫鍵



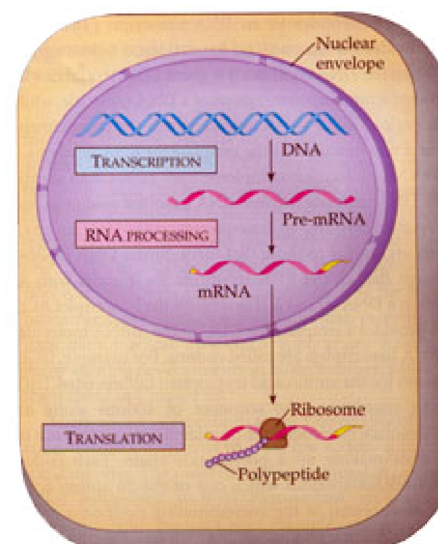
A - T

C - G





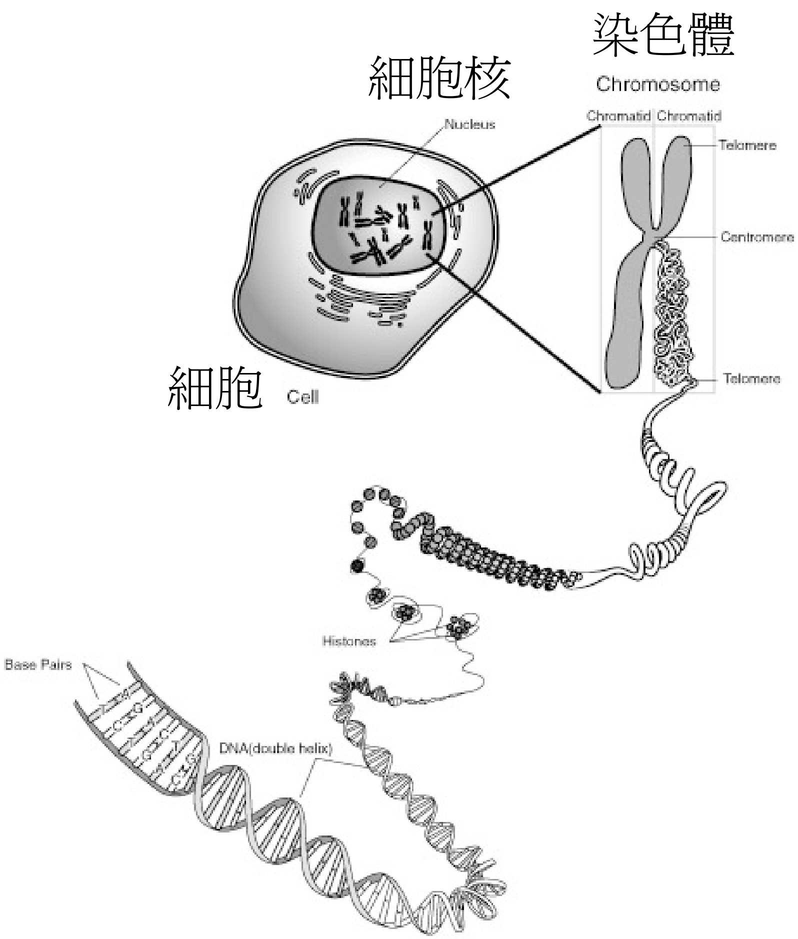
原核生物細胞



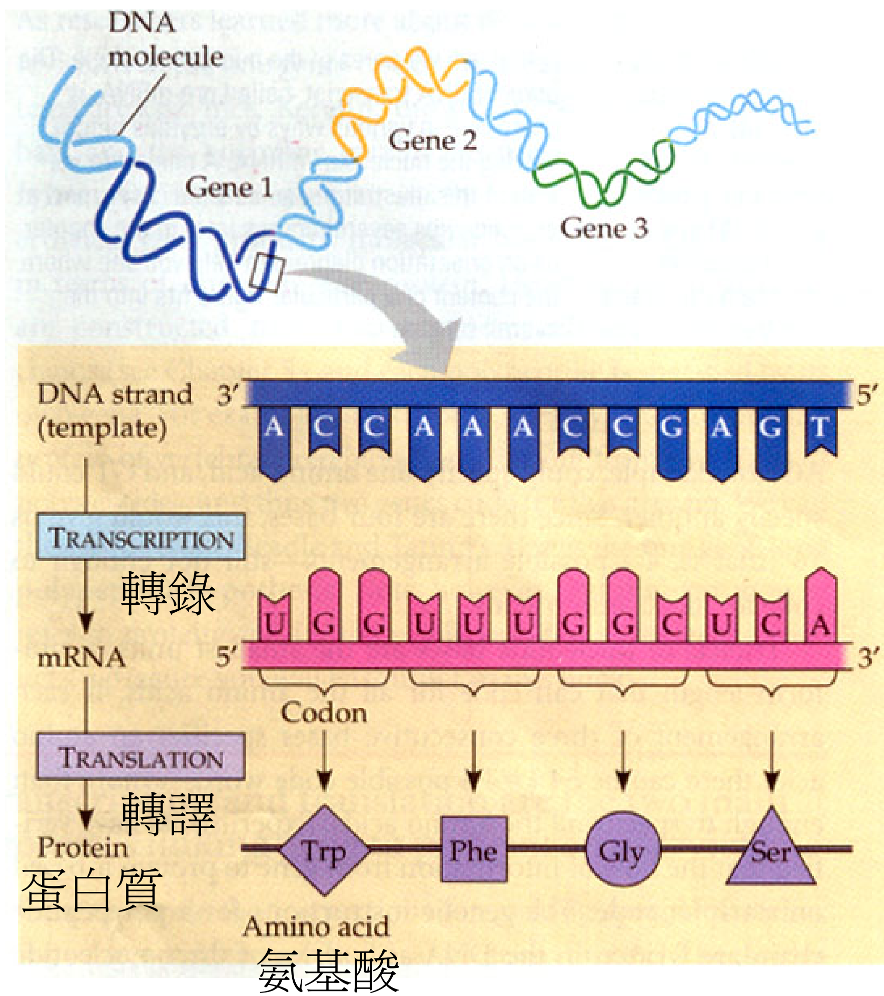
真核生物細胞

(Campbell, *Biology*)

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
基因的開啟與關閉- 時間與地點指令

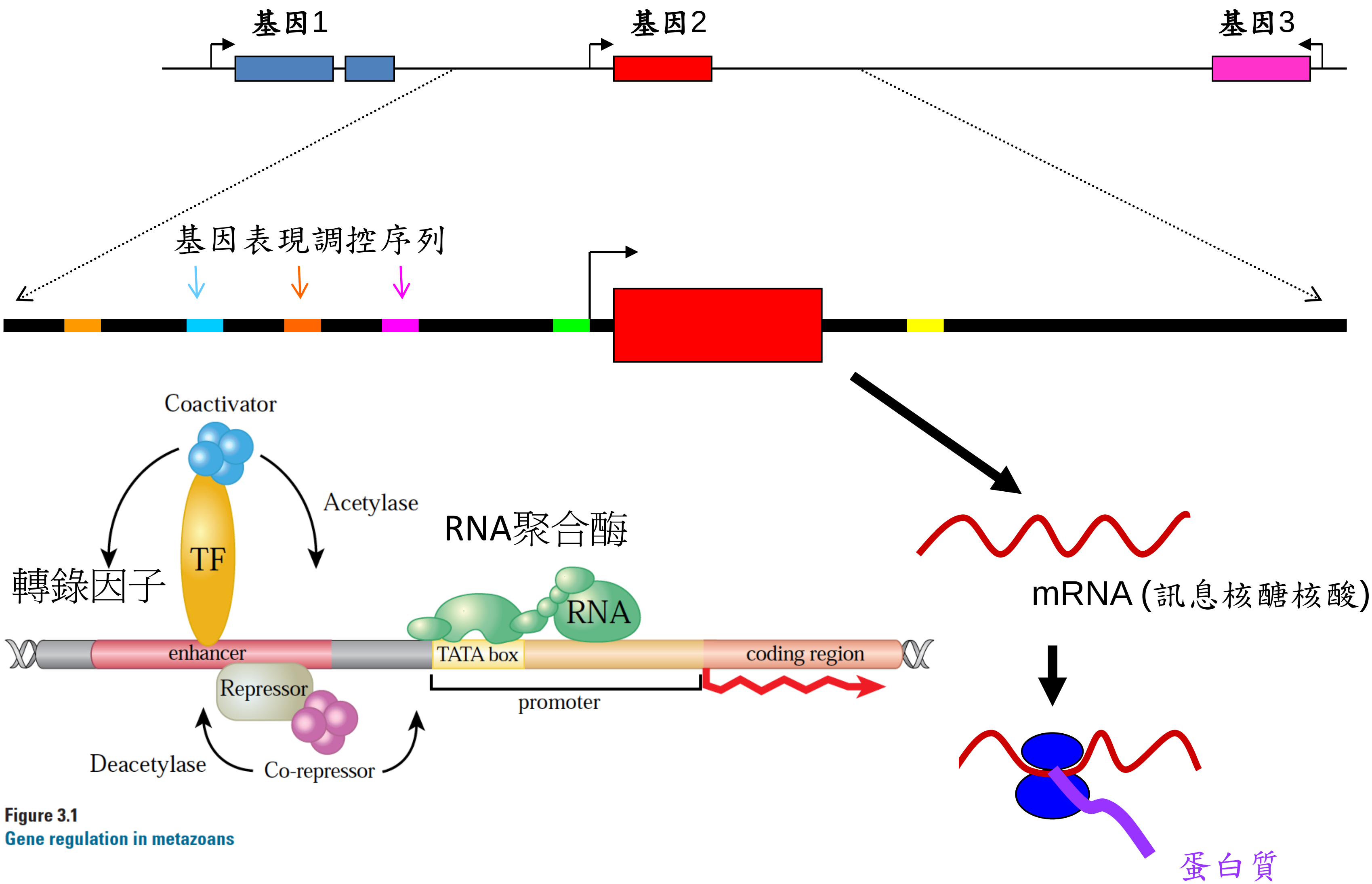
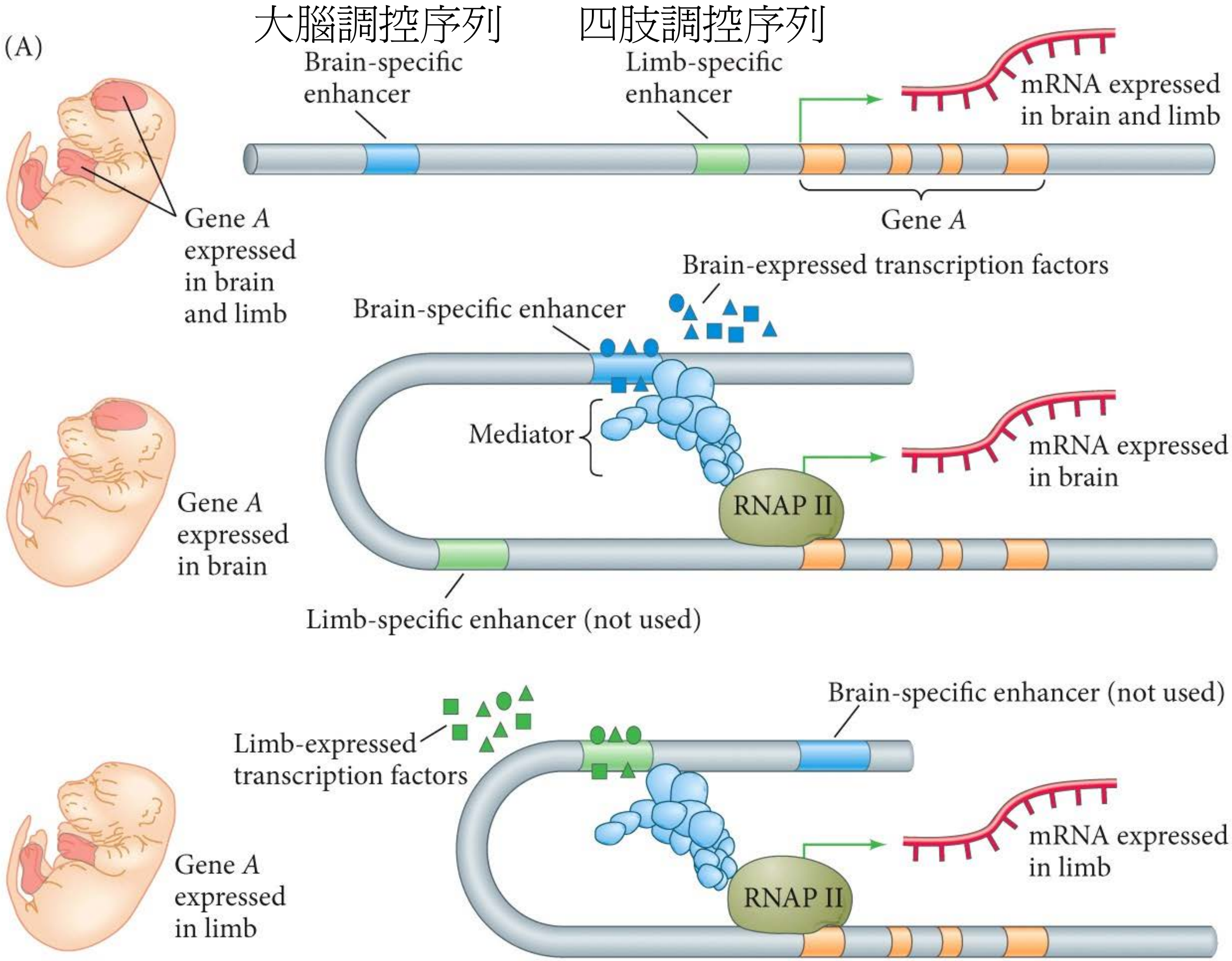


Figure 3.1
Gene regulation in metazoans

基因表現的調控－組織特異性的表現調控



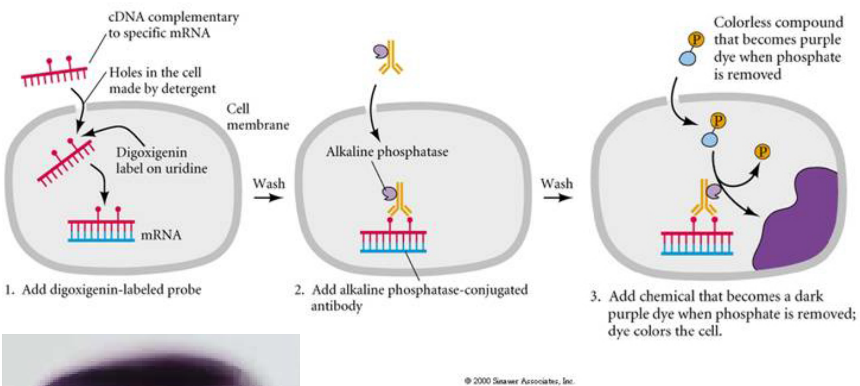
DEVELOPMENTAL BIOLOGY 10e, Figure 2.9 (Part 1)

大腦細胞內的轉錄因子會與大腦調控序列結合，開啓基因A在大腦表現

四肢細胞內的轉錄因子會與四肢調控序列結合，開啓基因A在四肢表現

Visualizing gene expression in developing animals

1. *In situ* hybridization: visualization of mRNA



SoxB expression in amphioxus CNS

2. Immunohistochemistry: visualization of protein

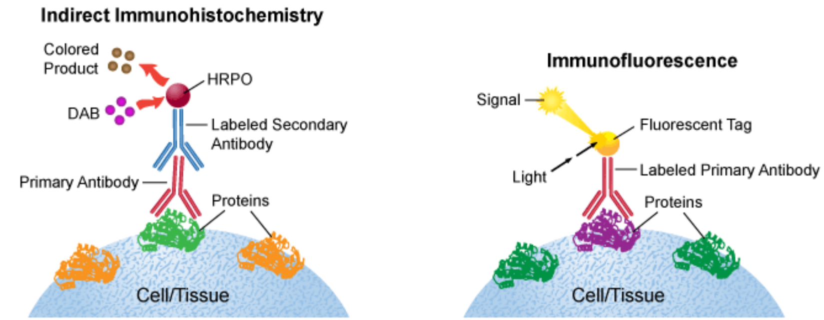
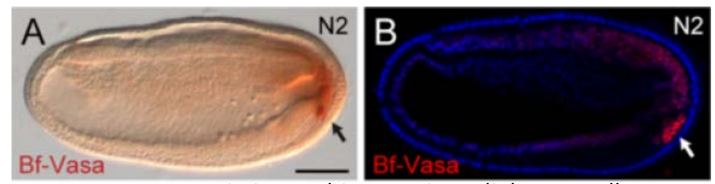
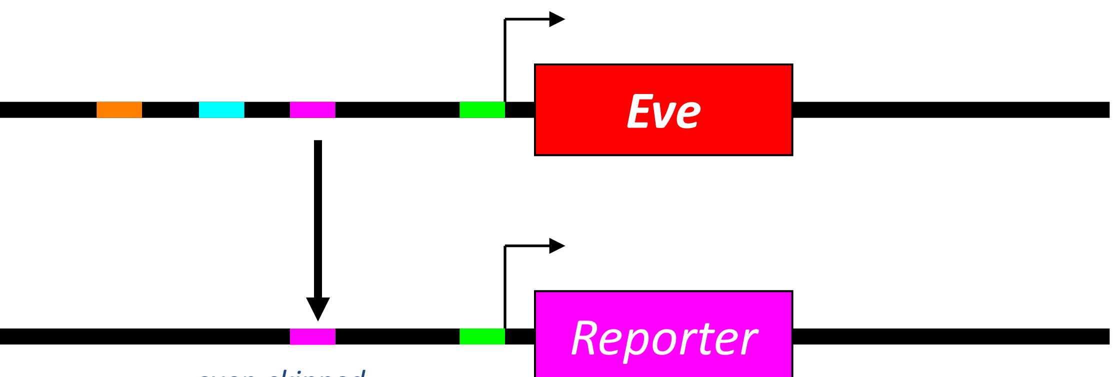


Diagram 1: *Illustration of Indirect Immunohistochemistry and Immunofluorescence methods.*



Vasa protein in amphioxus primordial germ cell

3. Reporter construct with cis-regulatory elements of specific gene



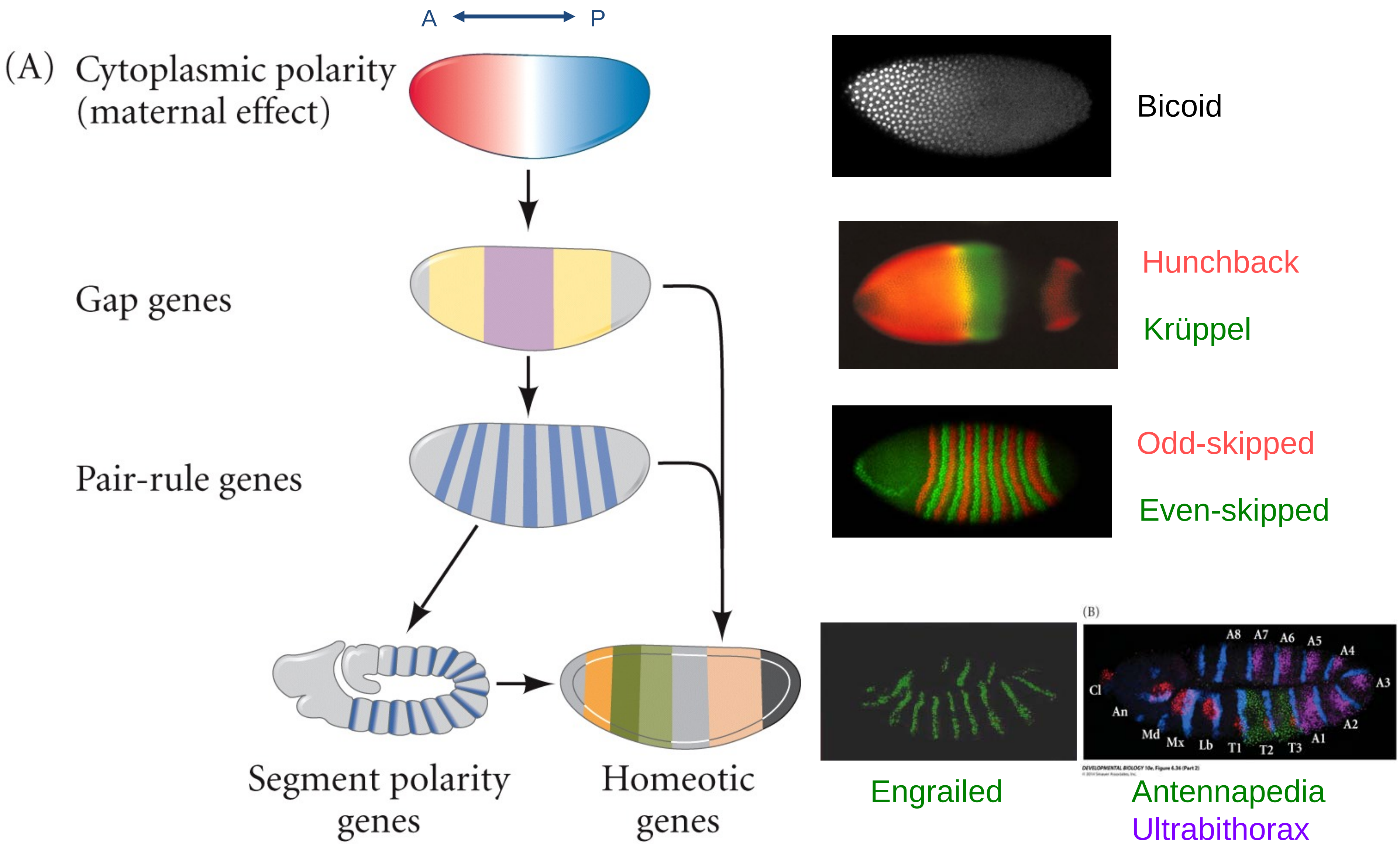
even-skipped
stripe 2 enhancer

Endogenous gene expression (*even-skipped* in fly embryo)

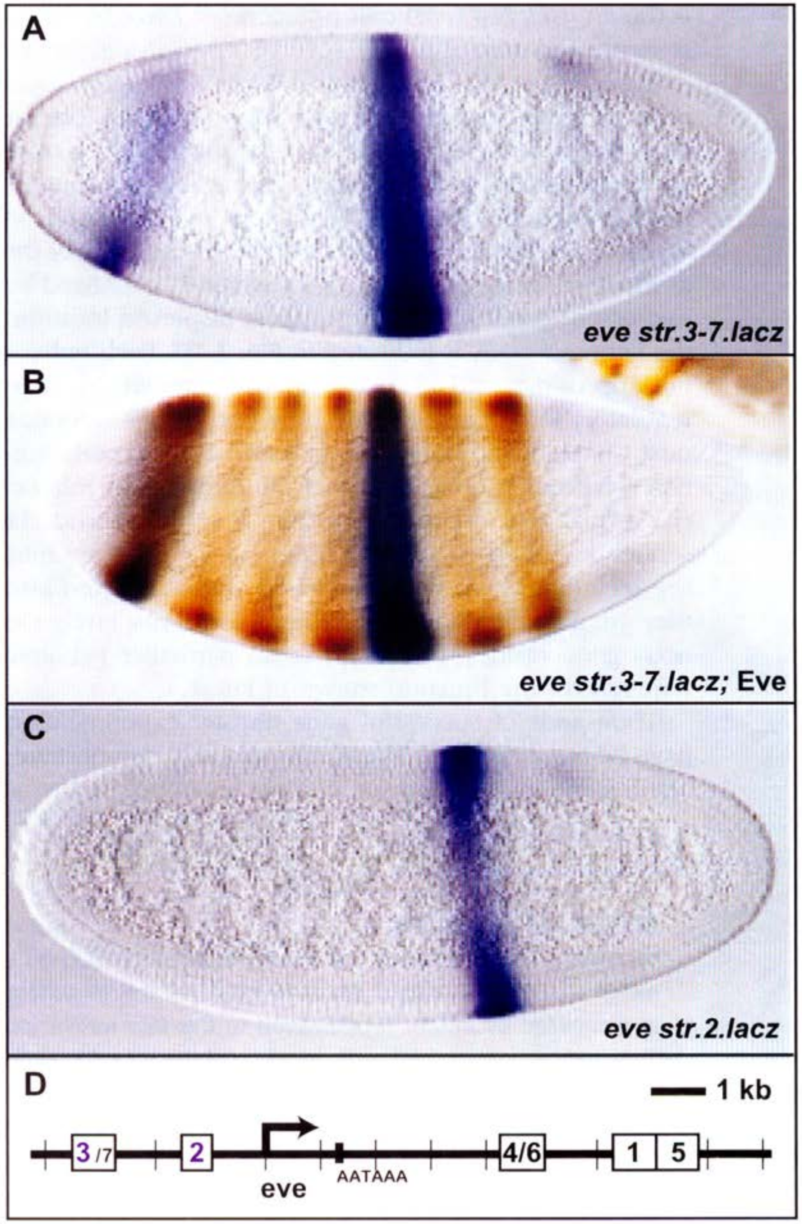
Reporter gene expression directed by tissue-specific enhancer (*even-skipped* stripe 2 enhancer)

(Modified from Small Blair & Levine, 1992)

發育過程的基因邏輯–以果蠅為例



DEVELOPMENTAL BIOLOGY 10e, Figure 6.18 (Part 1)



果蠅 evenskipped 基因的調控

Accurate expression of evenskipped (eve) stripe 2, and strips 3+7, generated by individual cis-regulatory elements.

A. Transgenic embryo carrying

B. Expression of endogenous eve gene plus reporter construct A

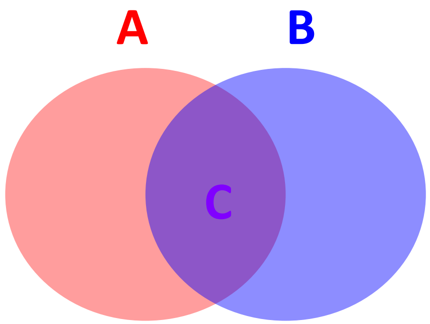
C. Transgenic embryo carrying

Davidson, 2006

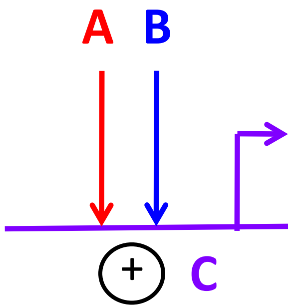
基因表現的調控邏輯

Cis-regulatory Design:

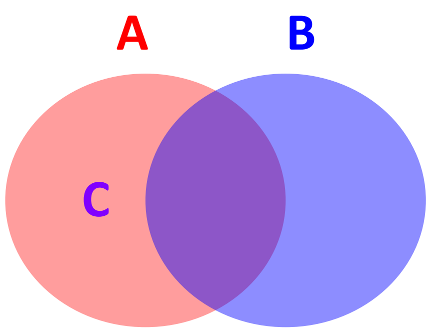
- **Integration of spatial inputs at the _cis_-regulatory level**



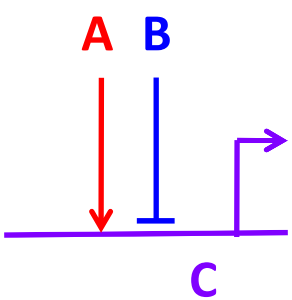
“AND” Logic



- **Repression of _cis_-regulatory design**

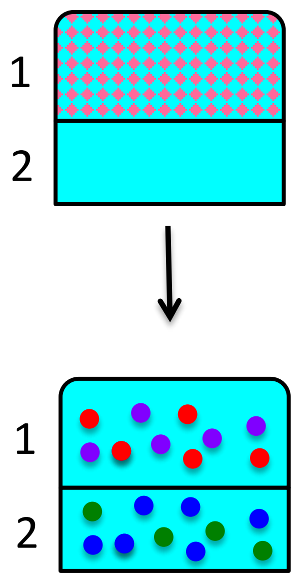


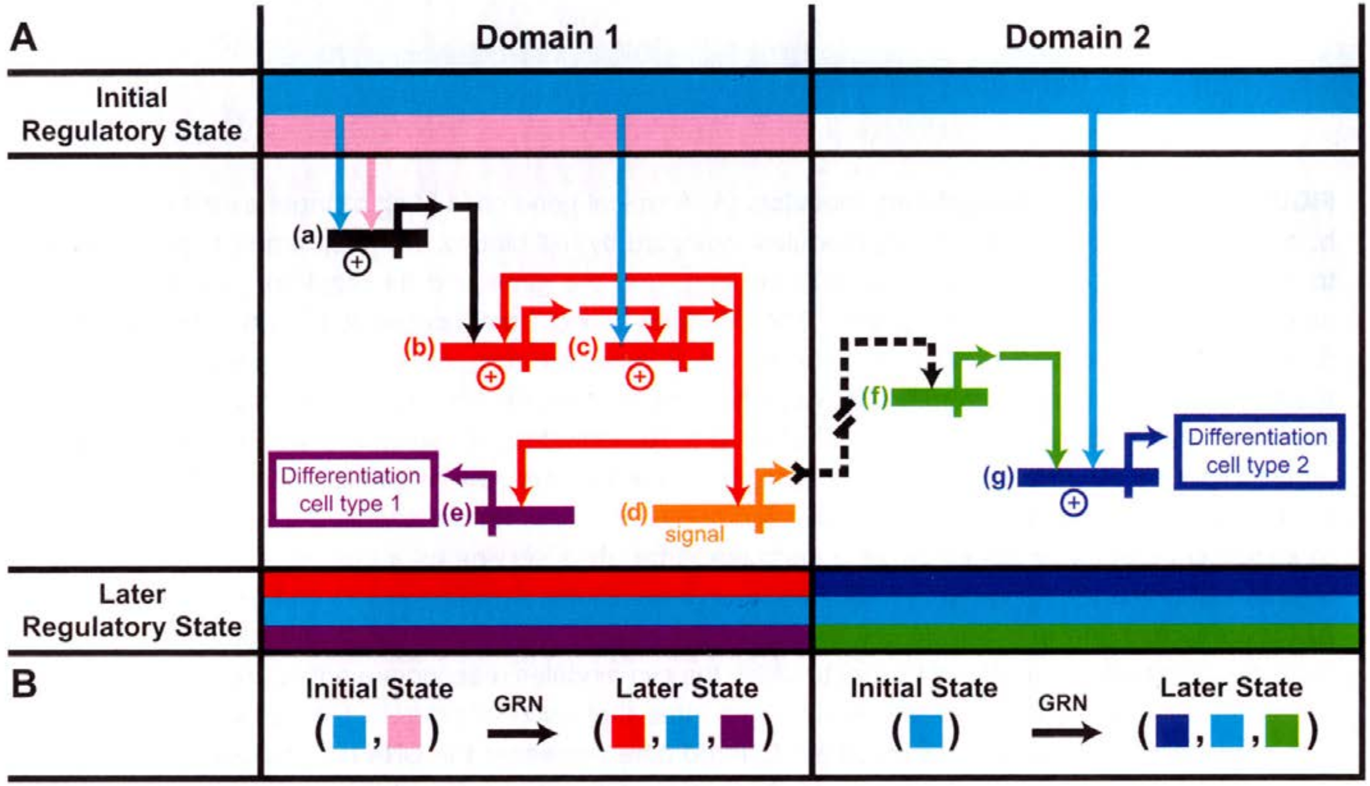
“OR” Logic



基因調控網路：
隨著發育的時間演進，胚胎各區域的組成漸漸不同

A hypothetical embryo with 2 domains



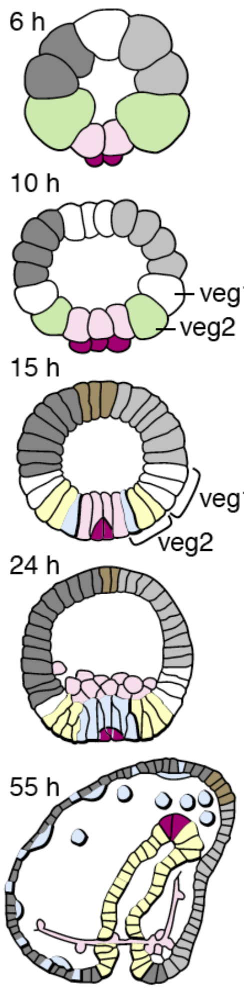


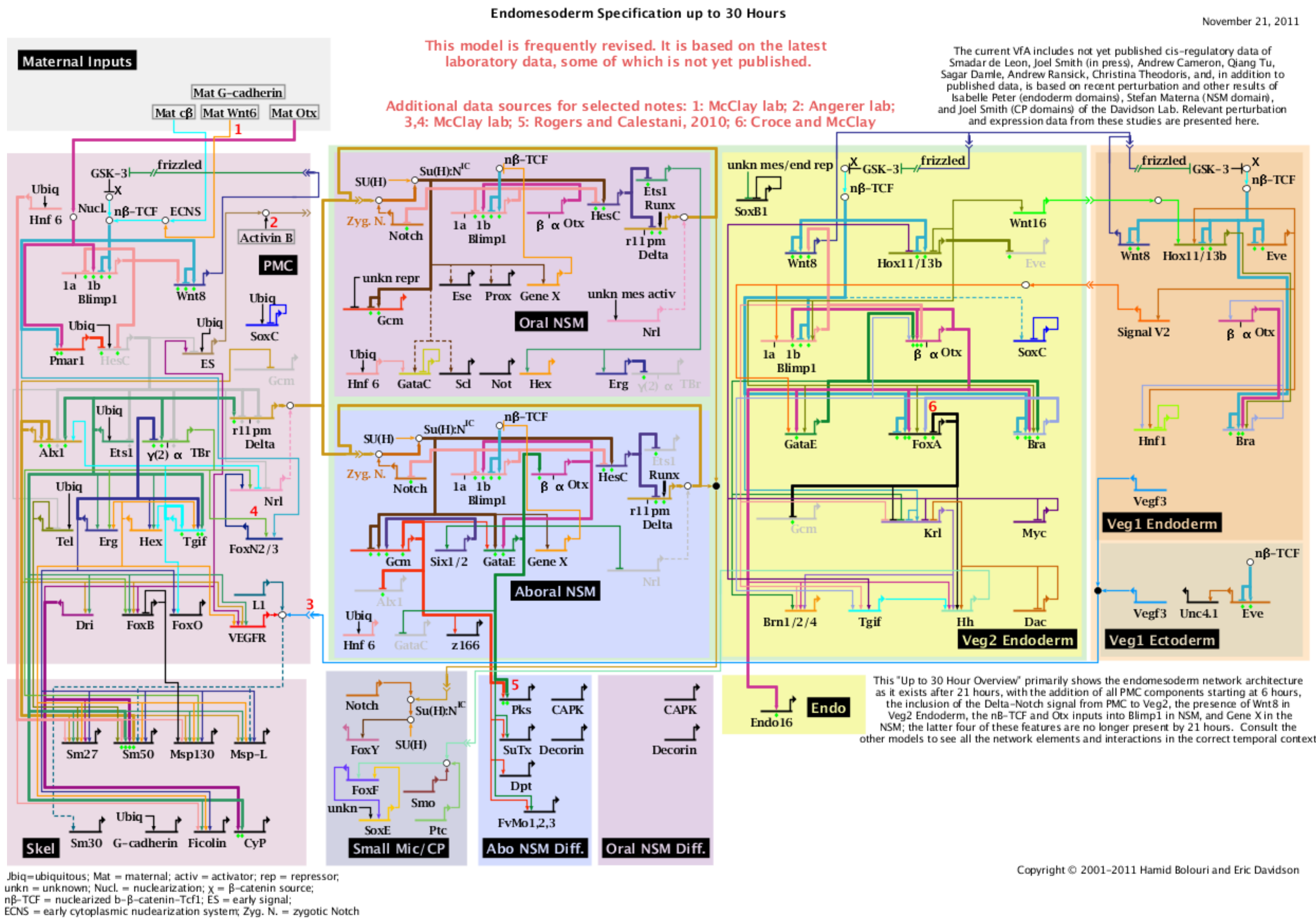
Davidson, 2006

- Two adjacent domains of an embryo
- Transcription factor and signal ligand genes
- Initial regulatory state: a postively TF and a transiently TF
- Positive feedback systems consisting of gene b and c (once the red system is activated, there is no further dependence on the initial transient input- generation of new state)
- The ligand encoded by gene d is received in domain 2 and provides input to gene f
- The outcome of operation of the GRN is to produce the later regulatory states

- Inputs/outputs
- "AND" logic processing

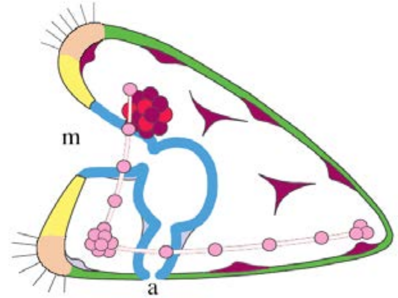
海膽胚胎的中內胚層發育基因調控網路



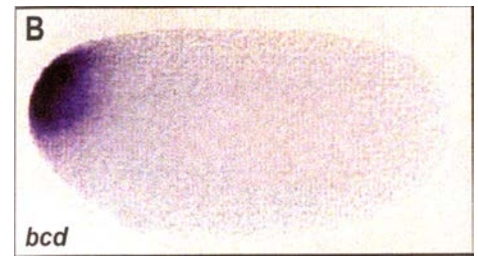


http://sugp.caltech.edu/endomes/#EndoNetworkDiagrams

Animal Development
動物的發育



Unequal distribution of mRNA and proteins (transcription factors and signaling molecules)
轉錄因子和訊息分子在早期胚胎的不均勻分布



Gene Regulation
基因調控

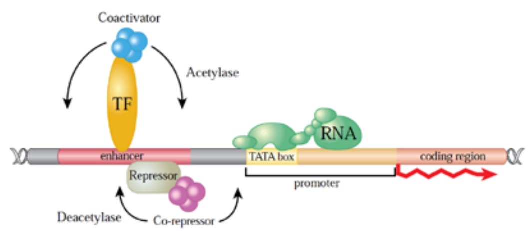
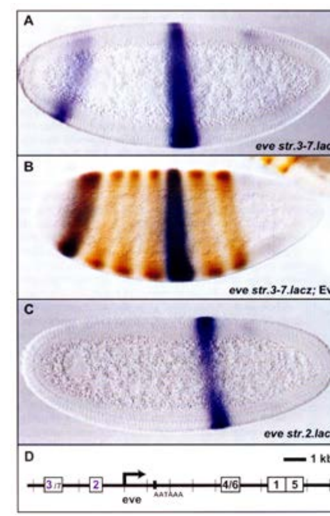


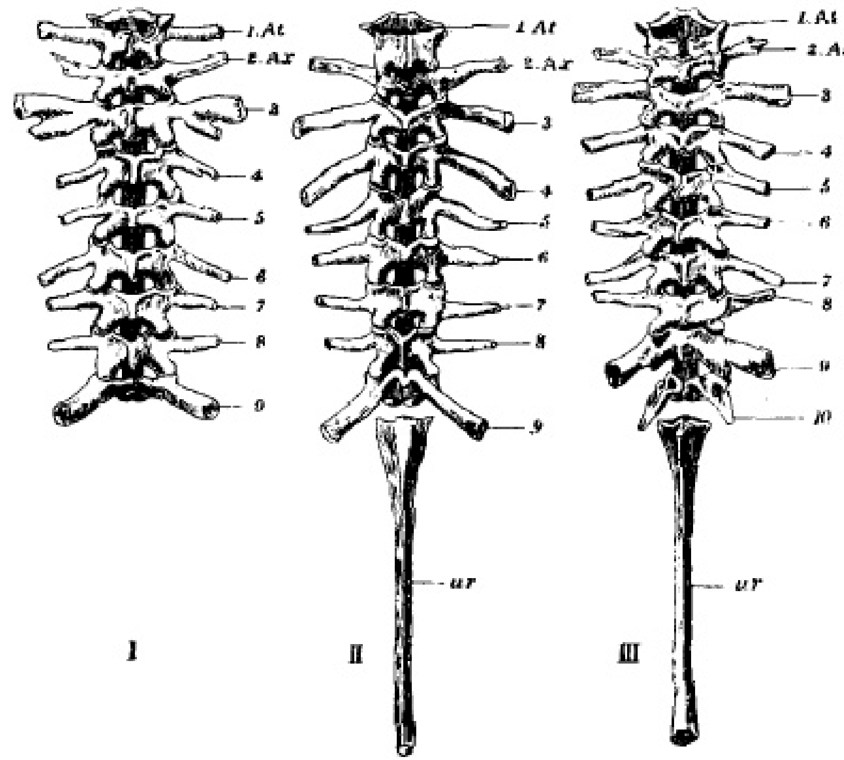
Figure 3.1
Gene regulation in metazoans

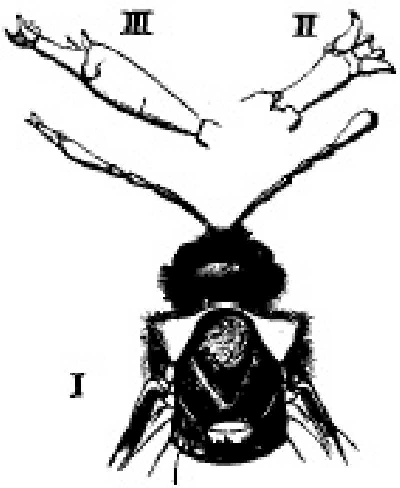
Cis-Regulatroy Elements
基因表現調控序列

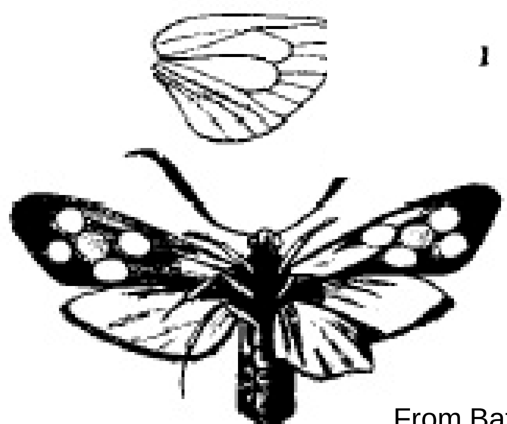


The Logic of Gene Regulation and Gene Regulatory Network
基因表現調控邏輯與基因調控網路

William Bateson: Homeotic transformation in animals (1894)







From Bateson 1894, ***Materials for the study of variation: treated with special regard to discontinuity in the origin of species***

果蠅的生命週期

Cellular membranes do not form until after the 13th nuclear division, superficial cleavage, **syncytial blastoderm**

Gastrulation: germ band extension and retraction

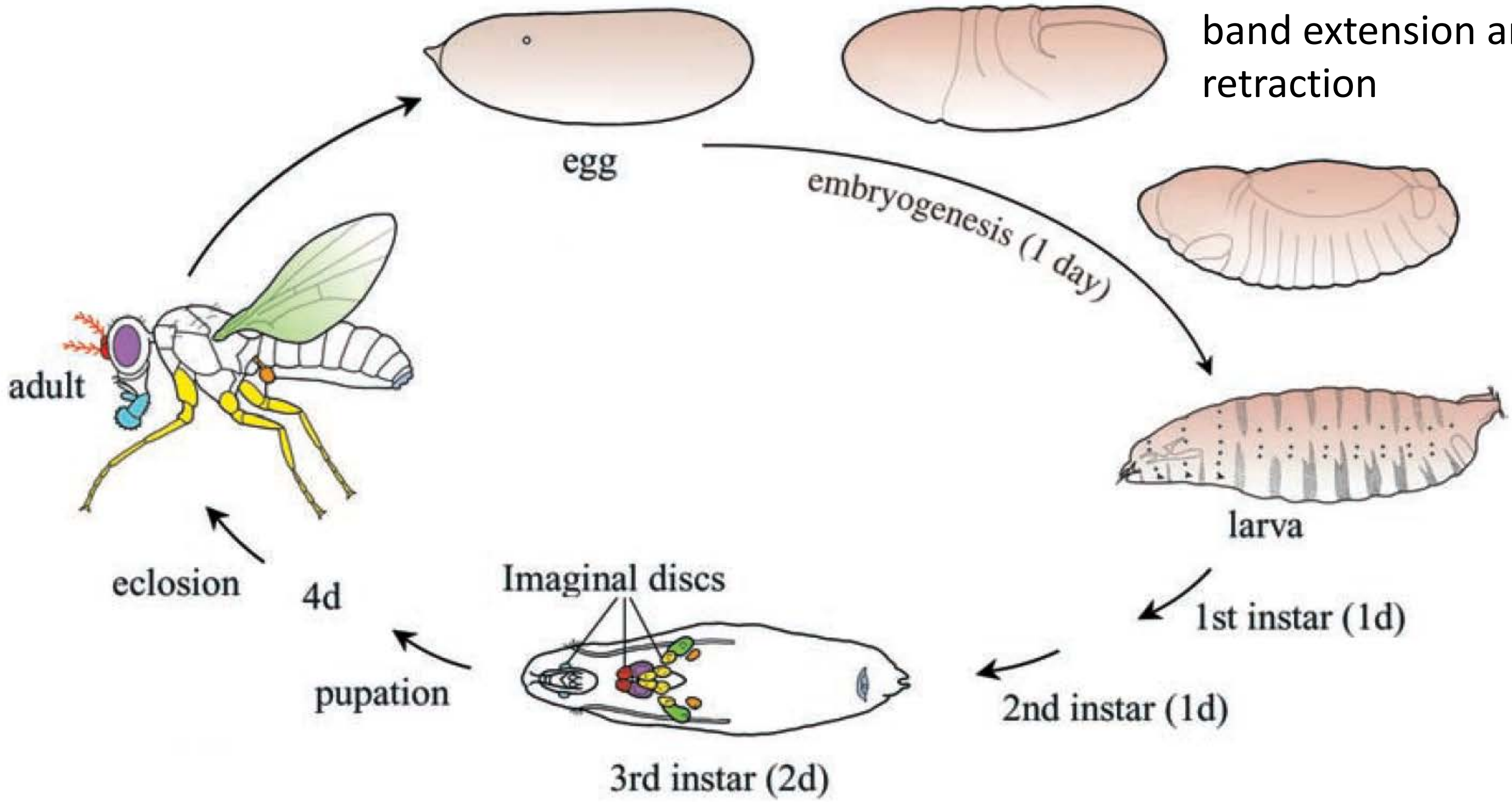
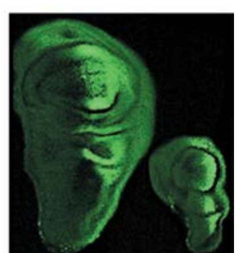
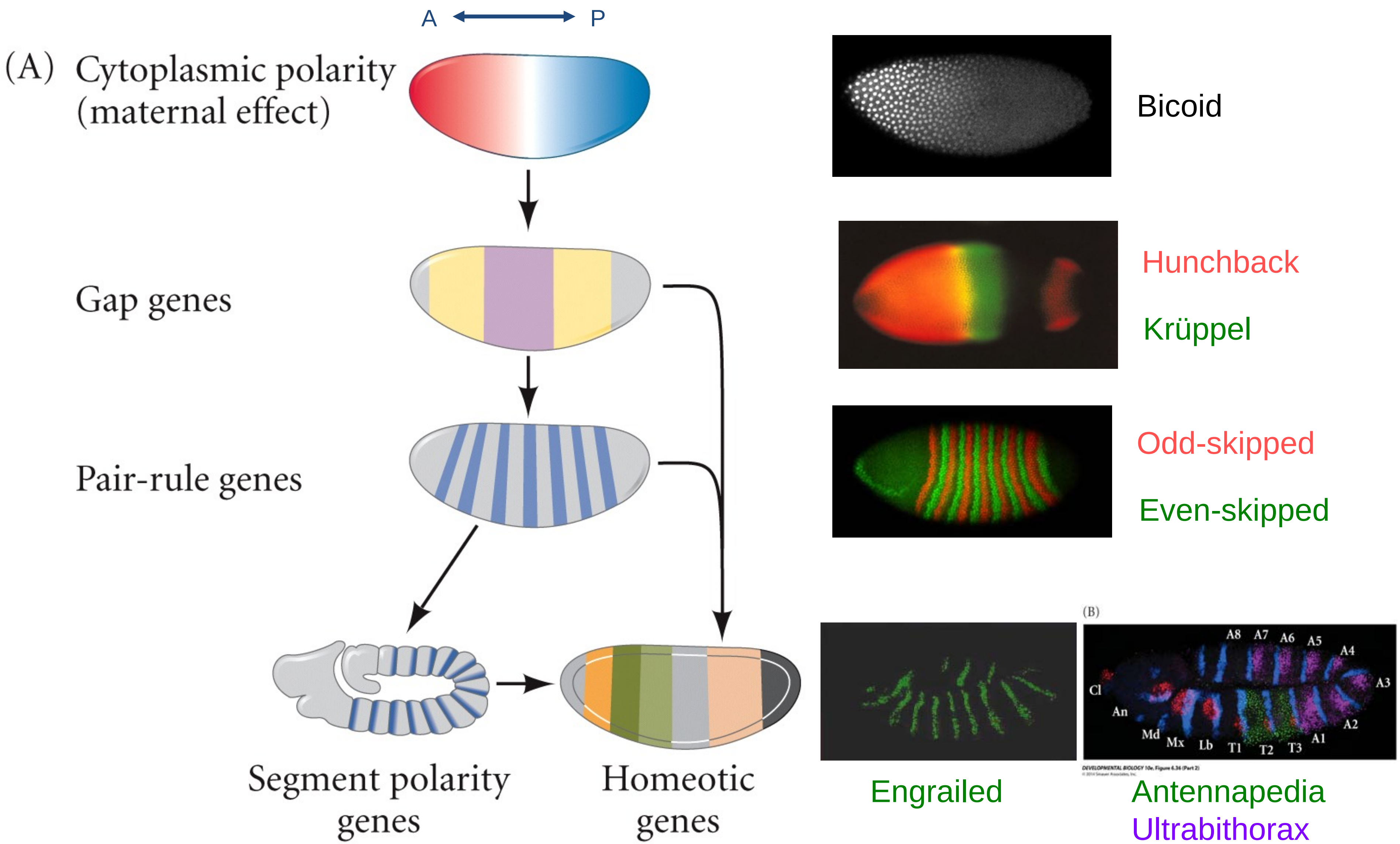


Figure 3.4
The *Drosophila* life cycle



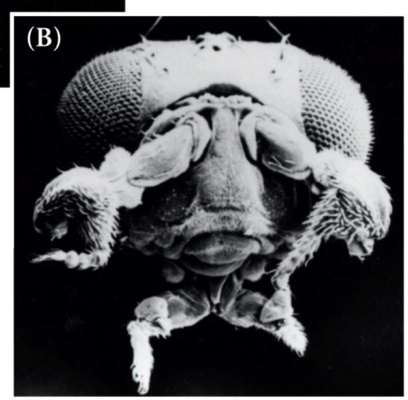
Wing and haltere imaginal discs

發育過程的基因邏輯—以果蠅為例



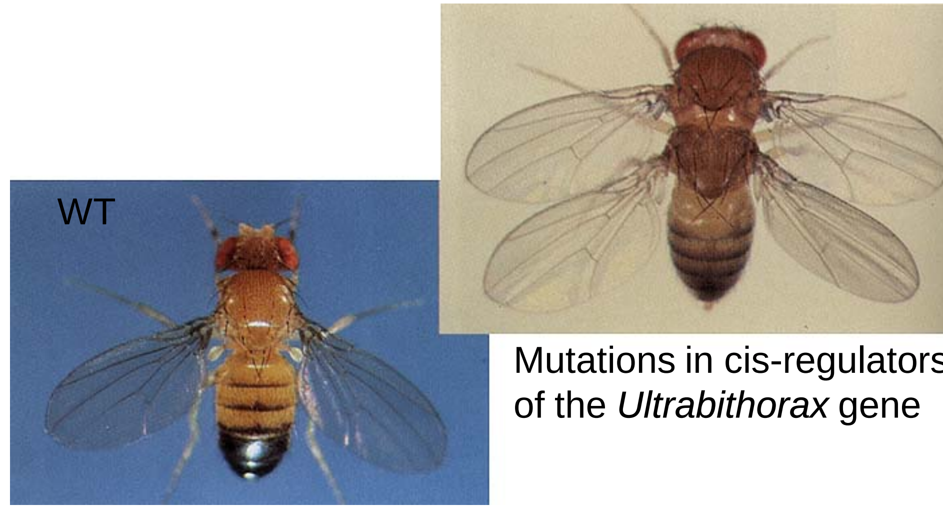
DEVELOPMENTAL BIOLOGY 10e, Figure 6.18 (Part 1)

Homeotic genes are used to specify segmental identity in *Drosophila*



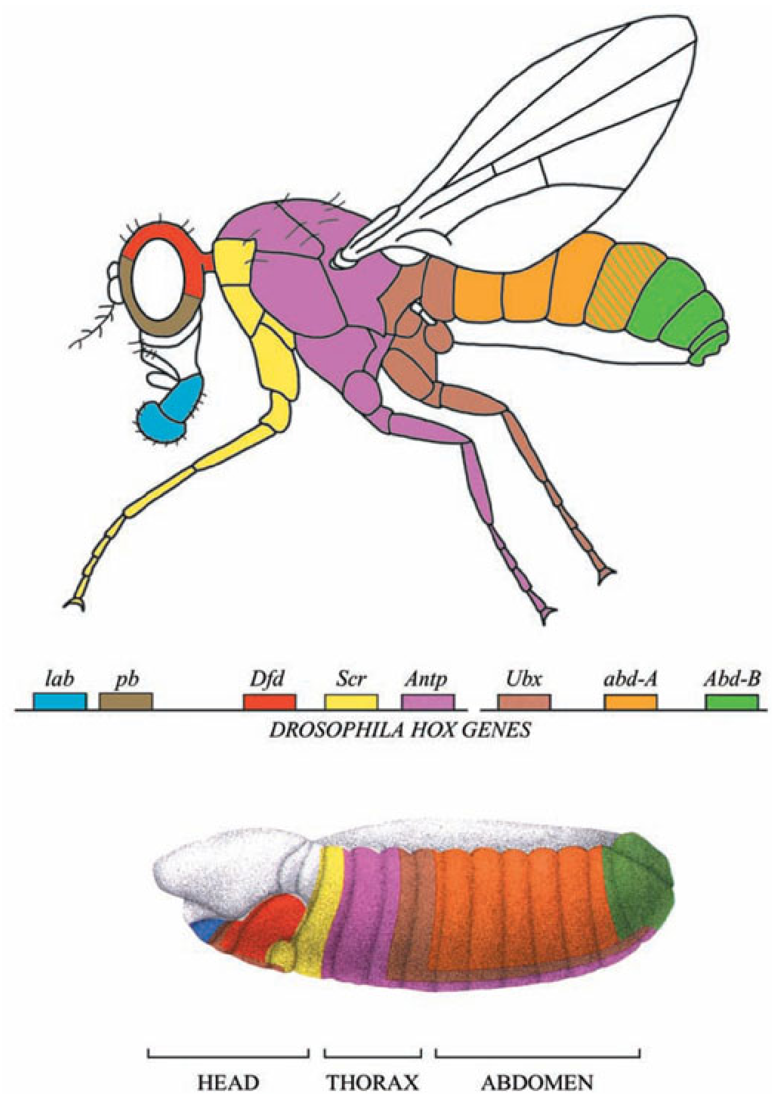
Antennapedia mutation

***DEVELOPMENTAL BIOLOGY 10e*, Figure 6.38**



Mutations in cis-regulators of the *Ultrabithorax* gene

Hox 基因在染色體上的排列順序和他們在胚胎的表現位置相關（沿著胚胎的前端至後端表現）



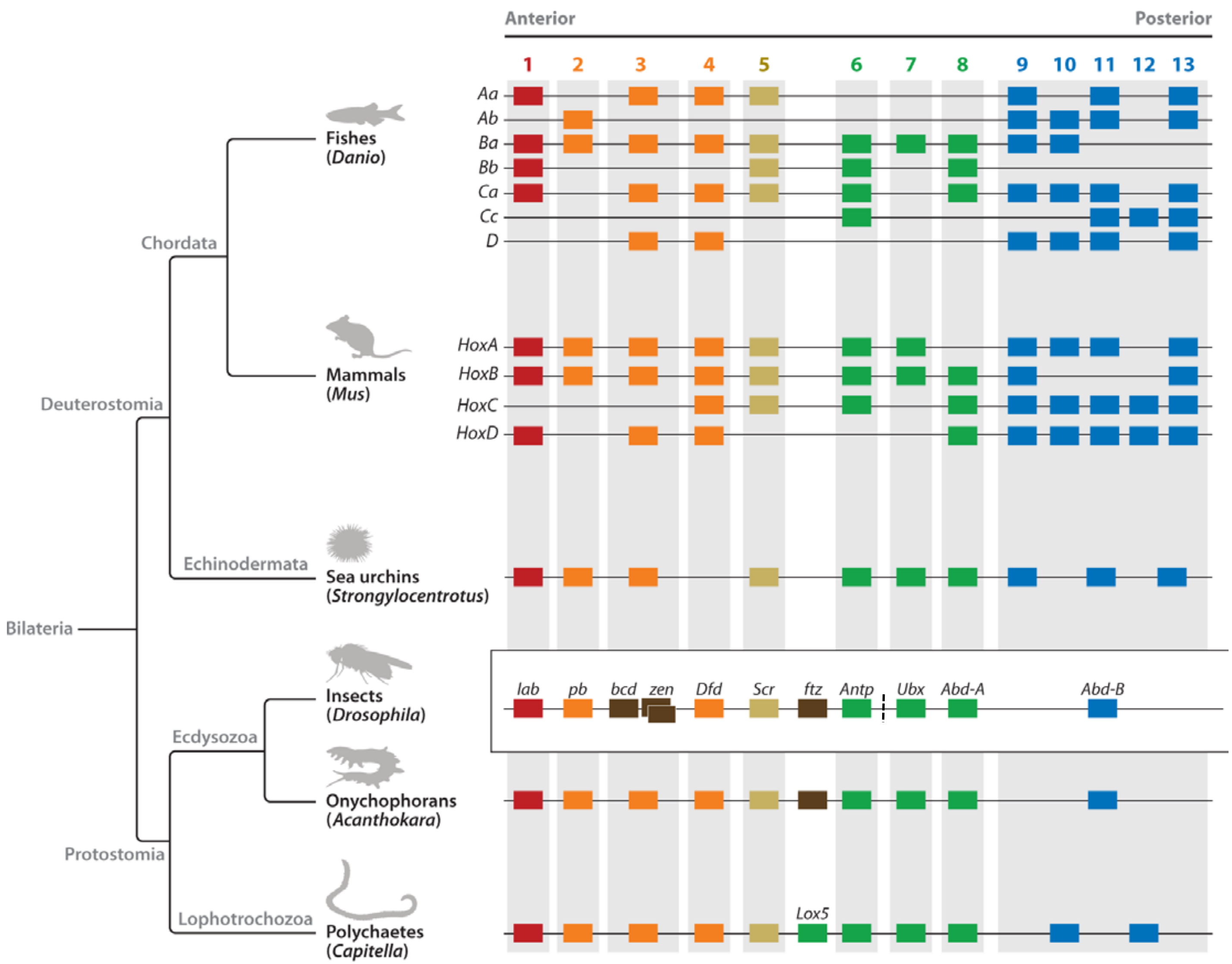
Hox 蛋白質是轉錄因子

Hox genes have a similar fragment of DNA (homeobox) that encodes a 60-amino acid protein domain

lab	NNSGRTNFTNKQLTELEKEFHFNRYLTRARRIEIANTLQLNETQVKIWFQNRRMKQKKRV
pb	PRRLRTAYTNTQLLELEKEFHFNKYLCRPRRIEIAASLDLTERQVKVWFQNRRMKHKRQT
Dfd	PKRQRTAYTRHQILELEKEFHYNRYLTRRRRIEIAHTLVLSERQIKIWFQNRRMKWKKDN
Scr	TKRQRTSYTRYQTLELEKEFHFNRYLTRRRRIEIAHALCLTERQIKIWFQNRRMKWKKEH
Antp	RKRGRQTYTRYQTLELEKEFHFNRYLTRRRRIEIAHALCLTERQIKIWFQNRRMKWKKEN
Ubx	RRRGRQTYTRYQTLELEKEFHTNHYLTRRRRIEMAHALCLTERQIKIWFQNRRMKLKKEI
abd-A	RRRGRQTYTRFQTLELEKEFHFNHYLTRRRRIEIAHALCLTERQIKIWFQNRRMKLKKEL
abd-B	VRKKRKPYSKFQTLELEKEFLFNAYVSKQKRWELARNLQLTERQVKIWFQNRRMKNKKNS
consensus	-RRGRT-YTR-QTLELEKEFHFNRYLTRRRRIEIAHALCLTERQIKIWFQNRRMK-KKE-

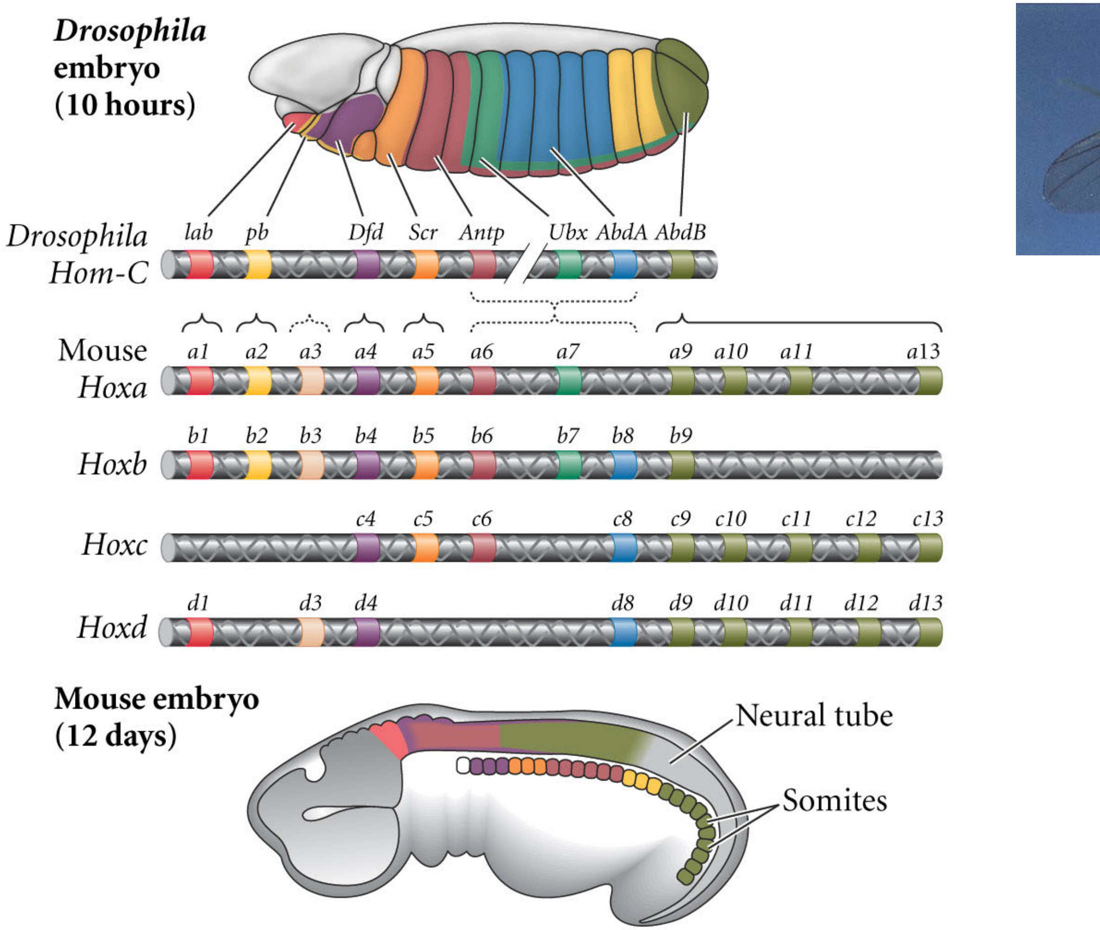
Helix 1　Helix 2　Helix 3

*Hox*基因廣泛存在於各類動物

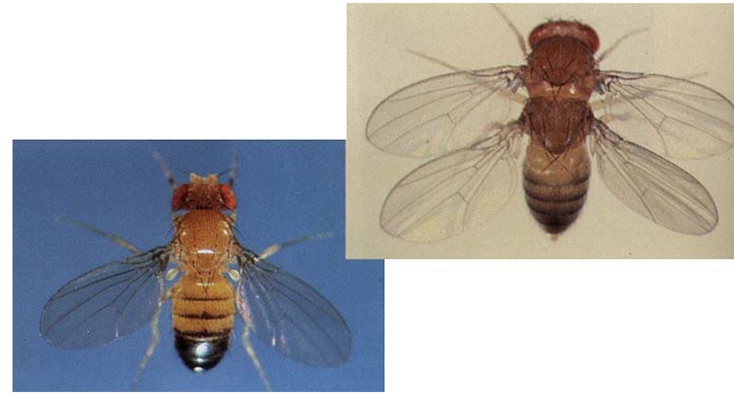


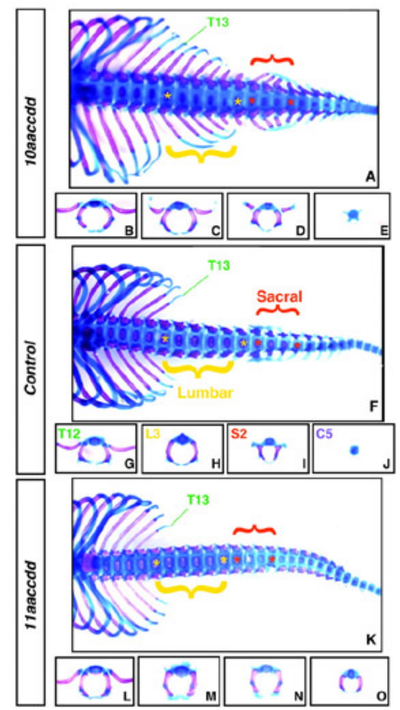
Heffer A, Pick L. 2013.
Annu. Rev. Entomol. 58:161–79

*Hox*基因調控動物前後體軸的發育



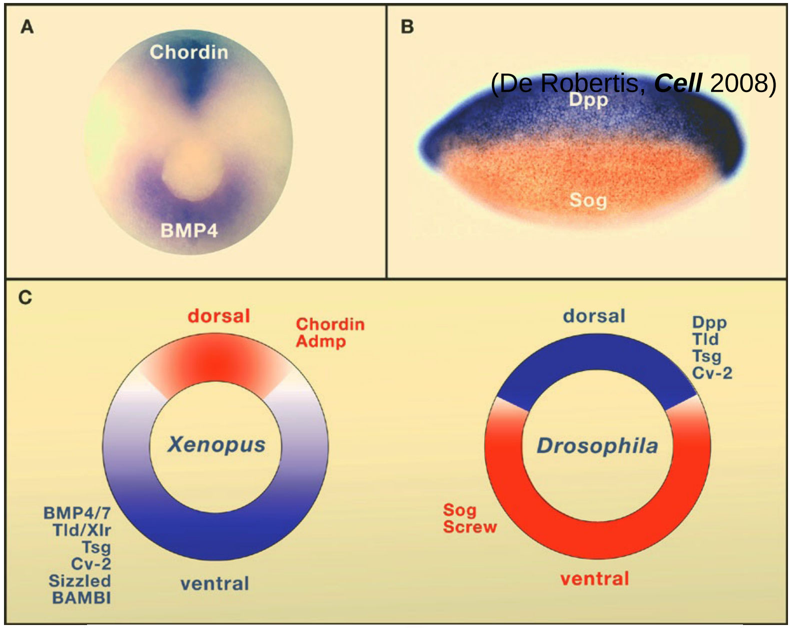
DEVELOPMENTAL BIOLOGY, Eighth Edition, **Figure 11.42** © 2006 Sinauer Associates, Inc.

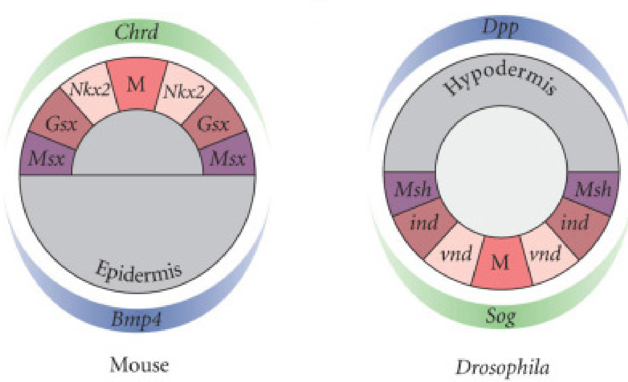


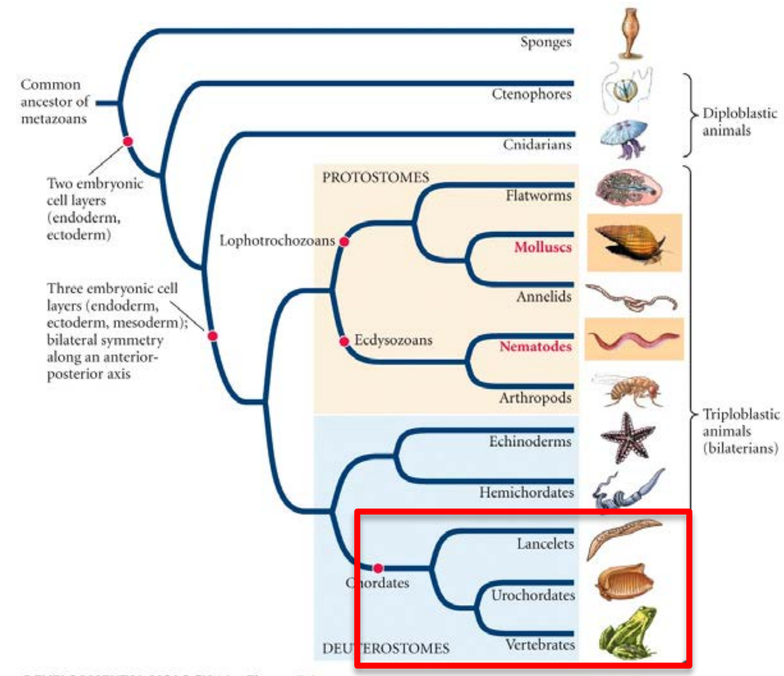


(Carroll et al, ***From DNA to Diversity***, 2001)

Conserved signaling system involved in D-V patterning between arthropods and chordates





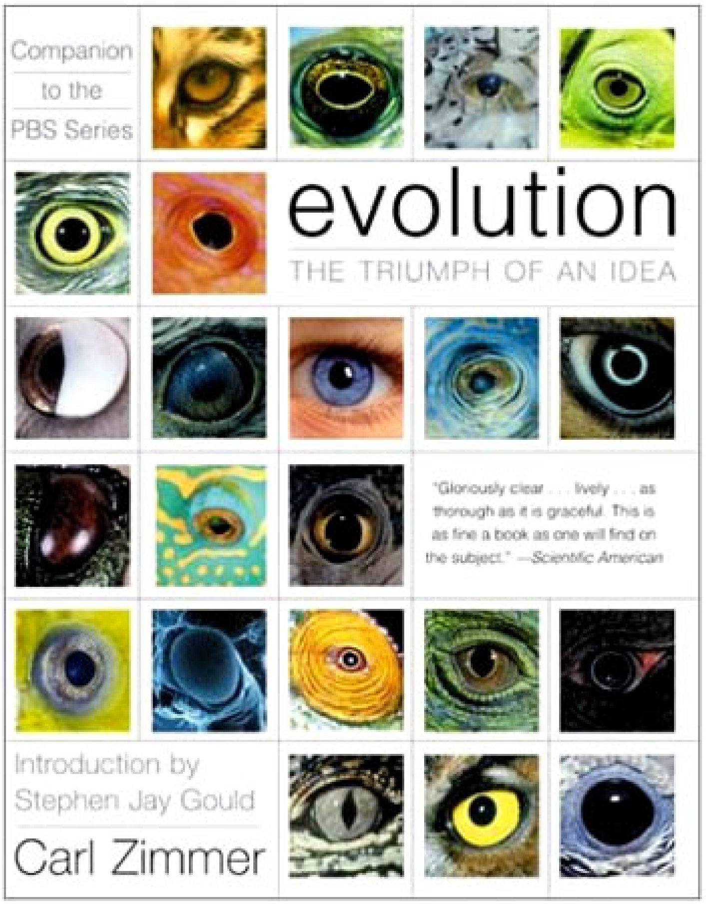


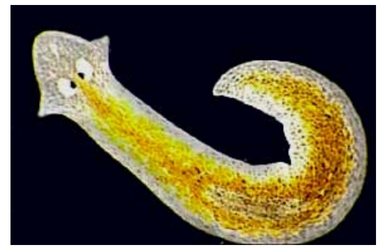
DEVELOPMENTAL BIOLOGY 10e, Figure 5.1

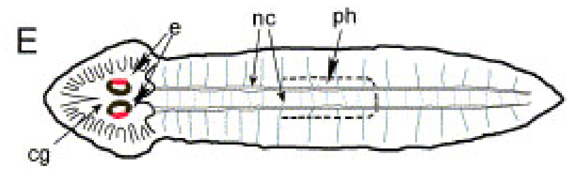
Inversion of BMP-Chordin axis?

The same set of genes patterns the CNS of both protostomes and deuterostomes

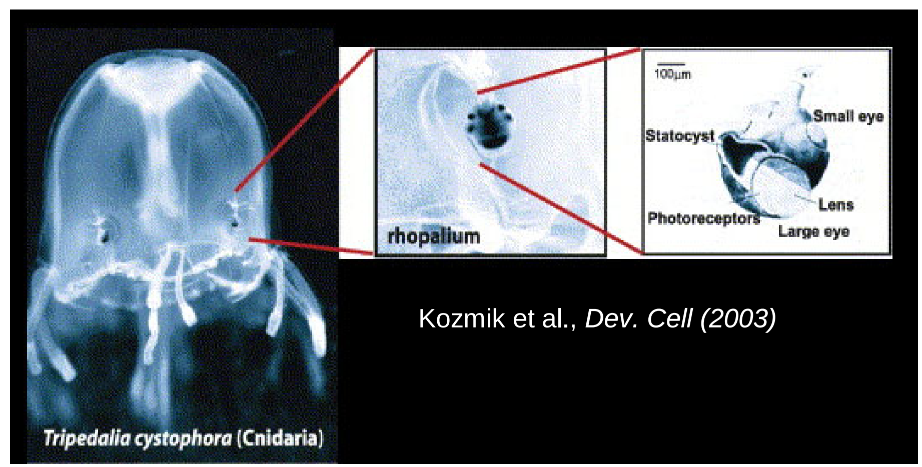
各式各樣的“眼睛”





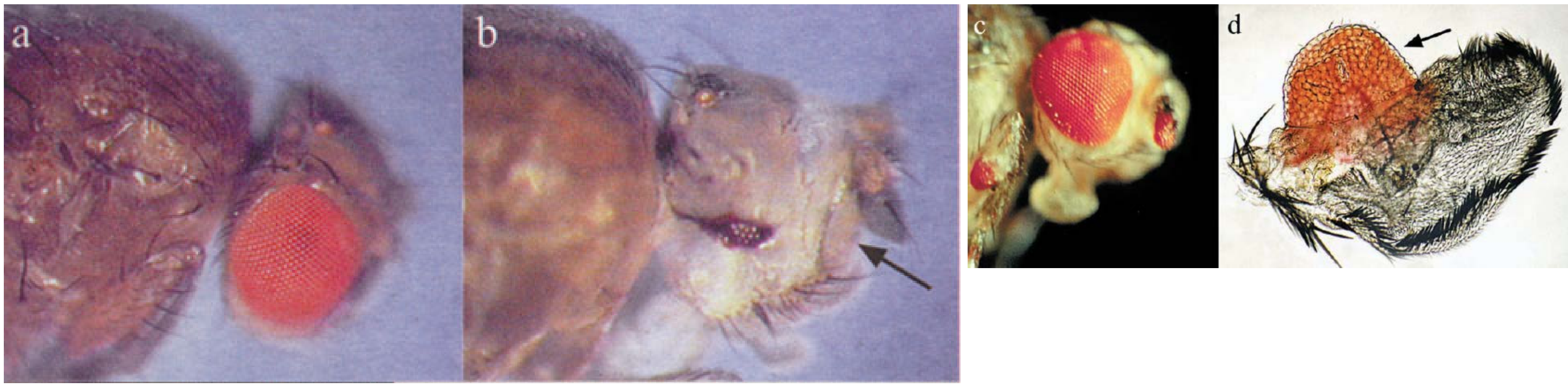


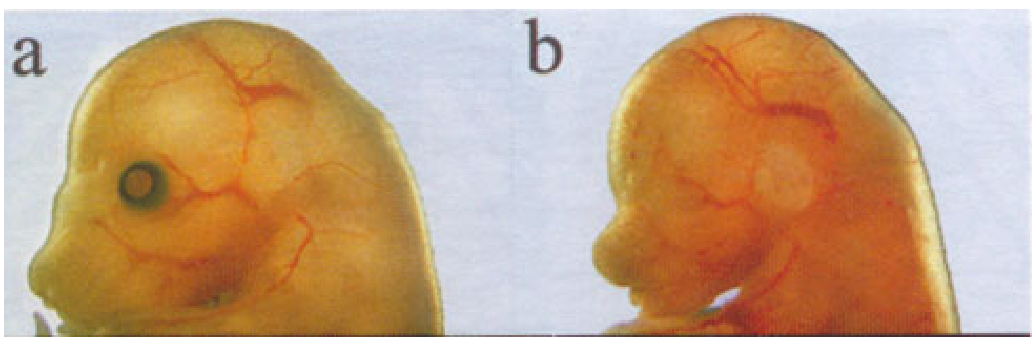
Mannini et al., *Dev. Biol (2004)*



Kozmik et al., *Dev. Cell (2003)*

Pax-6 基因調控動物眼睛的發育





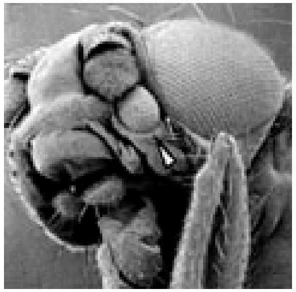
(Carroll, *From DNA to Diversity*, 2001)

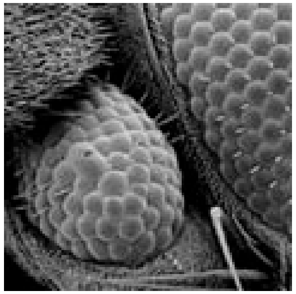
(Mouse Genome Database)

果蠅與老鼠的眼睛發育都受到這個同源基因的調控

果蠅的*Pax-6* 基因誘導眼睛的發育

(Halder et al. 1995)

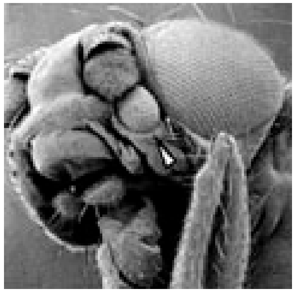


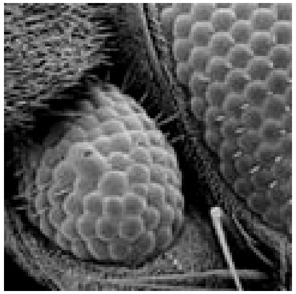


果蠅 *Pax-6*

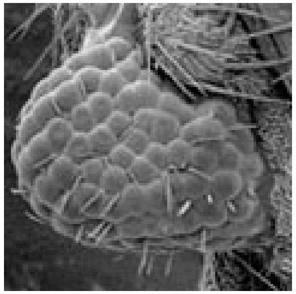
果蠅與老鼠的*Pax-6* 基因在眼睛發育的功能上是可以互相置換

(Halder et al. 1995)





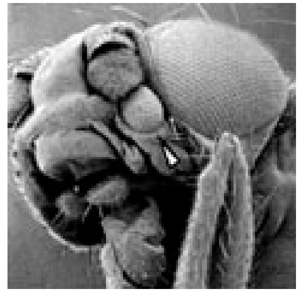
果蠅 *Pax-6*

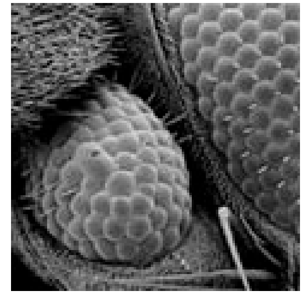


老鼠 *Pax-6*

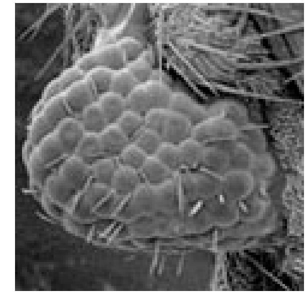
果蠅與老鼠的*Pax-6* 基因在眼睛發育的功能上是可以互相置換

(Halder et al. 1995)



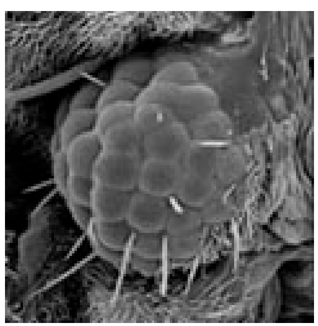


果蠅 *Pax-6*

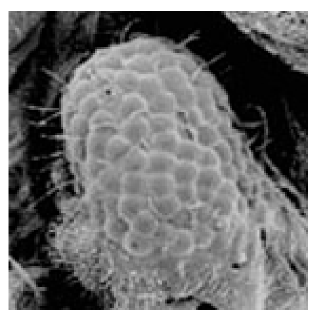


老鼠 *Pax-6*

更多不同動物的*Pax-6* 基因也可以在果蠅身體誘發眼睛發育



烏賊 *Pax-6*
(Tomarev et al. 1997)

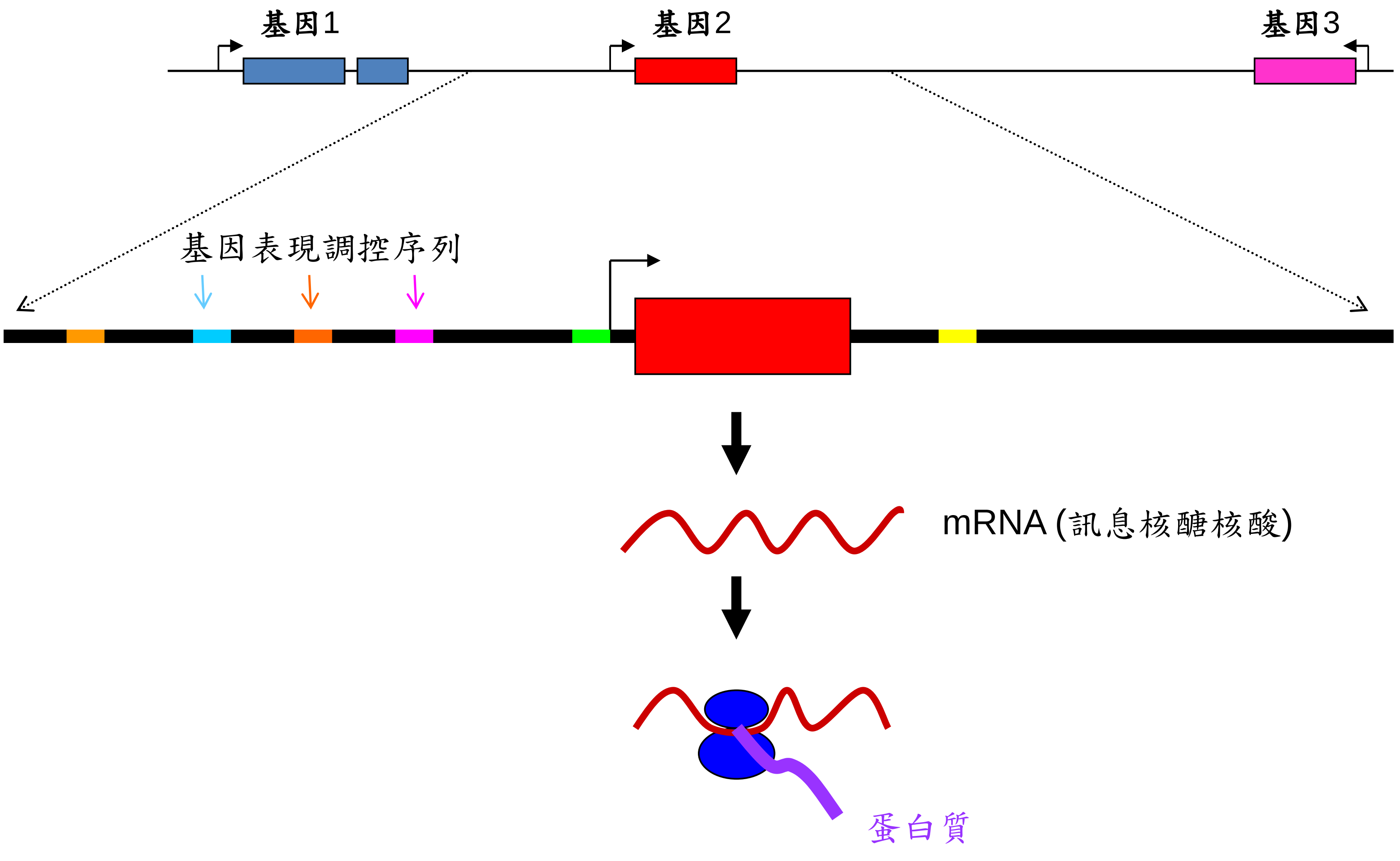


海鞘 *Pax-6*
(Glardon et al. 1997)

水母 *PaxB*
(Kozmik et al. 2003)

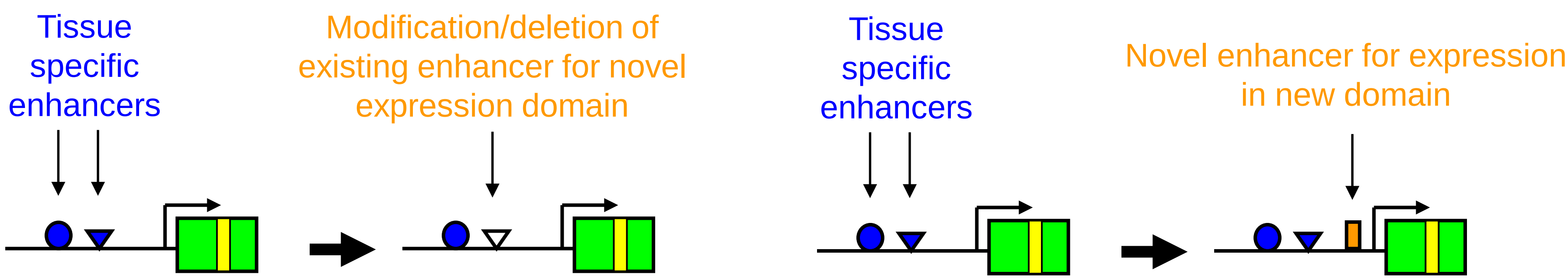
- 如果不同動物的基本身體結構發育是由相似的同源基因來調控，動物如何演化出如此歧異的形態?
- 我們是否能從發育基因與發育機制演化的角度來探討動物形態變異的起源?

發育基因如何演化出新的功能?

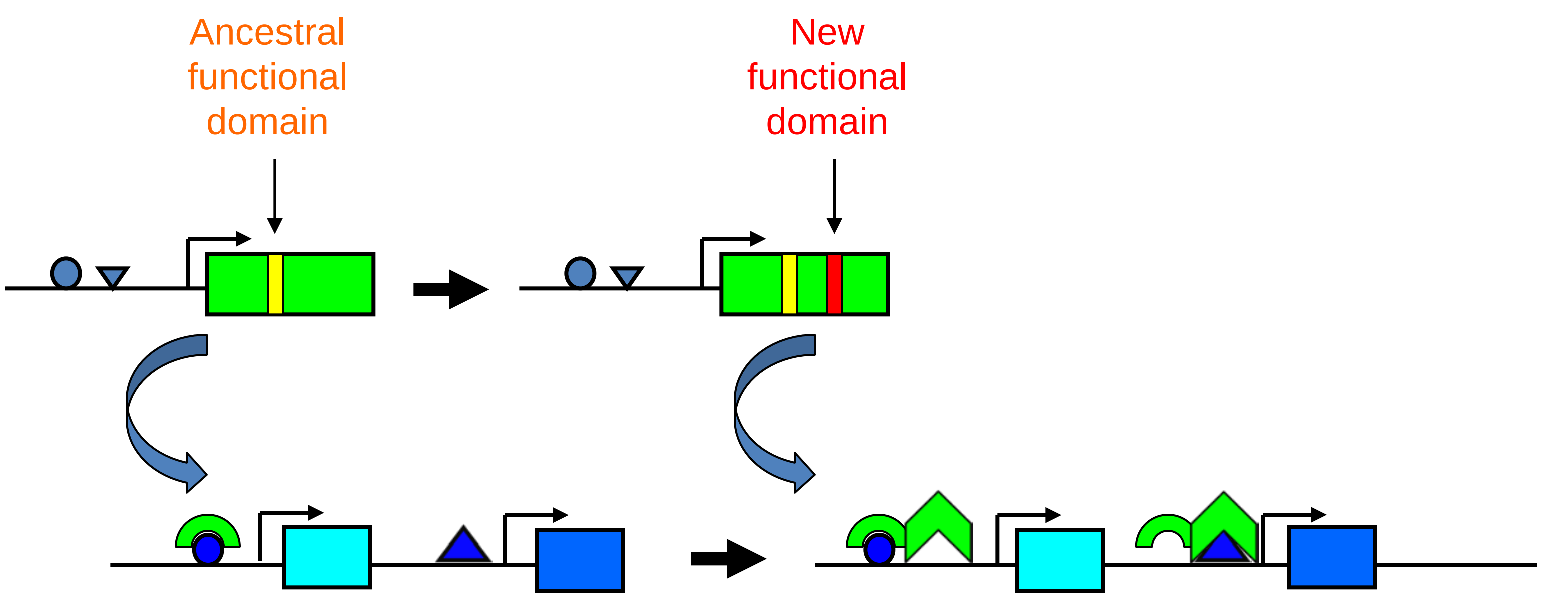


發育基因如何演化出新的功能?

1. 基因表現調控序列的演化造成基因表現方式的改變



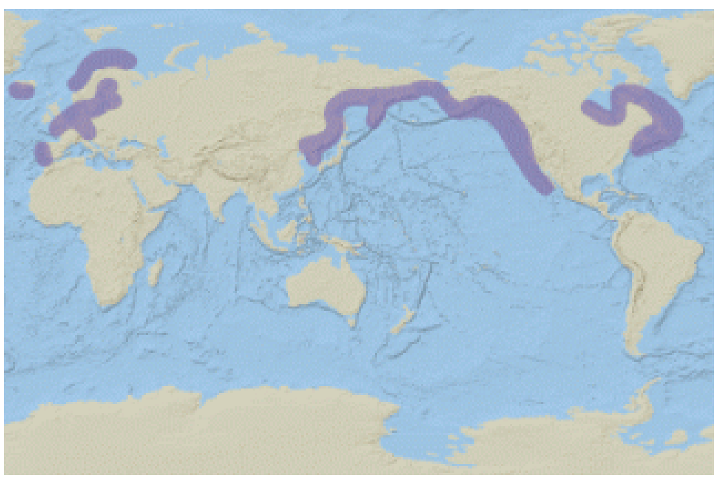
2.蛋白質序列的演化造成基因功能的改變

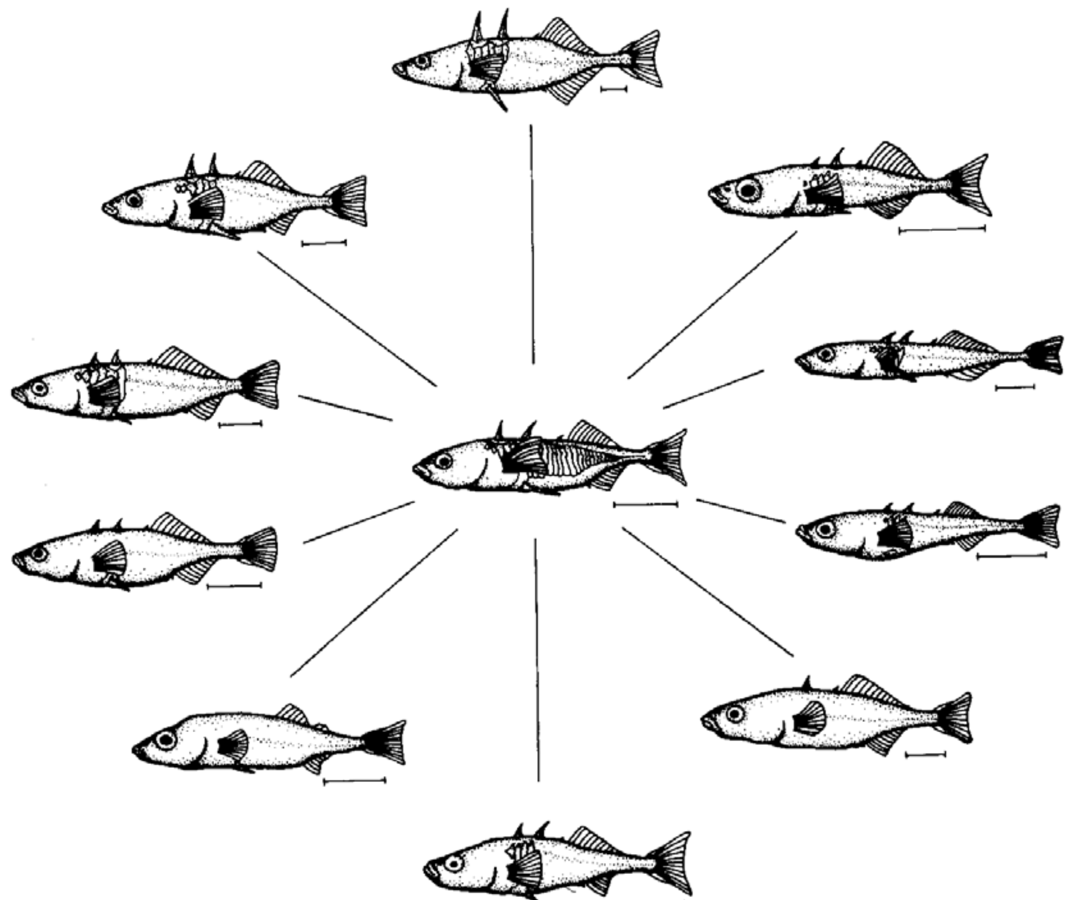


背棘魚形態的演化

在距今約 12,000 年前，一些原本在海水中生活的背棘魚進入淡水水域生活，並且演化出許多不同的形態，例如腹鰭的改變與消失

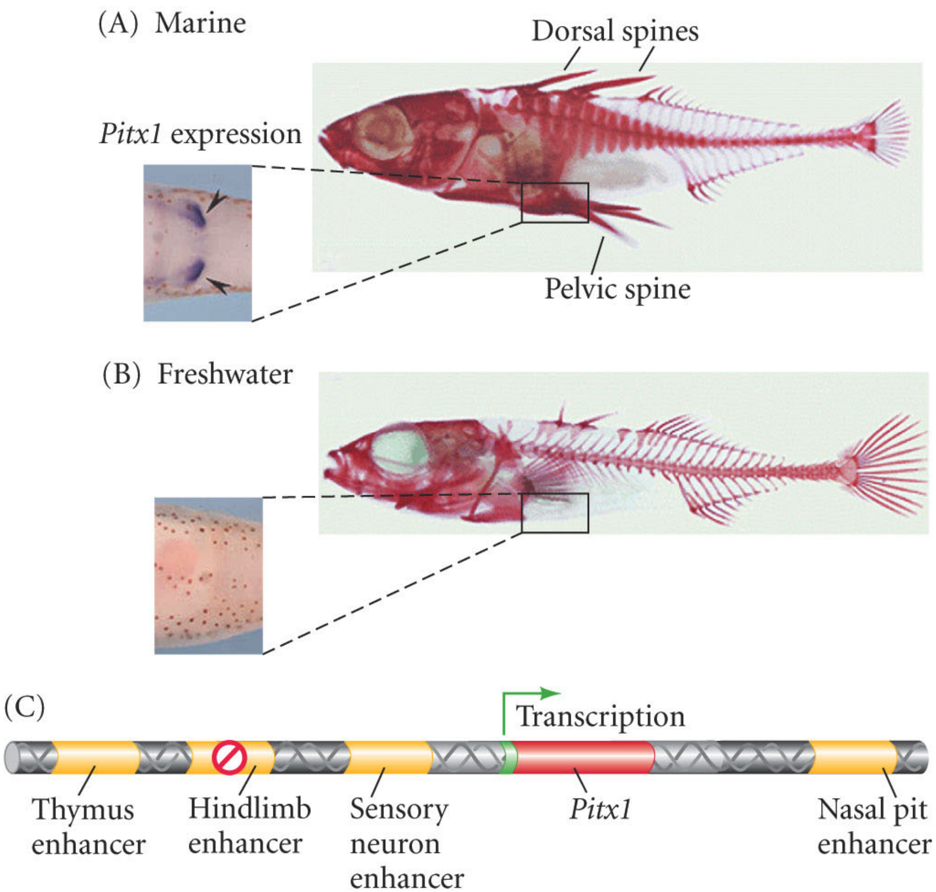
Threespine stickleback (*Gasterosteus aculeatus*)





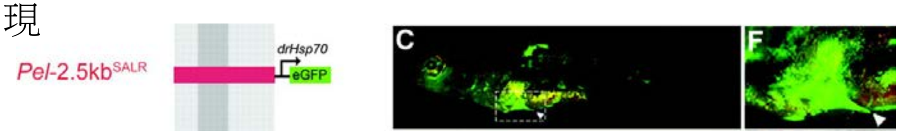
Bell and Foster 1994

背棘魚腹鰭的消失與 *Pitx1* 基因的表現有關

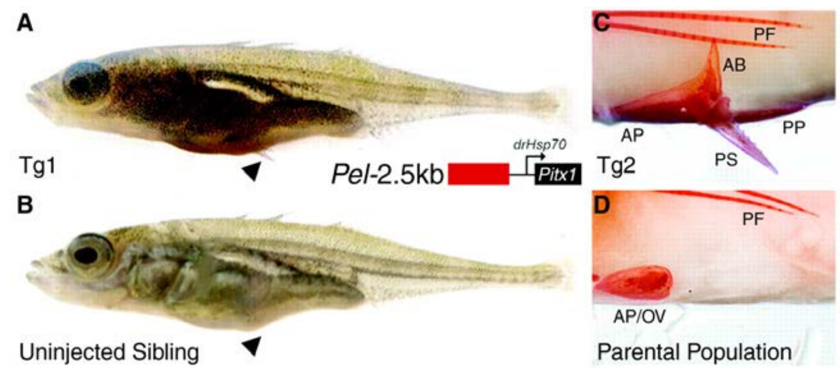


DEVELOPMENTAL BIOLOGY, Eighth Edition, Figure 23.3

研究人員從有腹鰭的海水背棘魚中找到一段 2.5-kb *Pitx1* intergenic DNA 可以調控腹鰭生長區域的基因表現

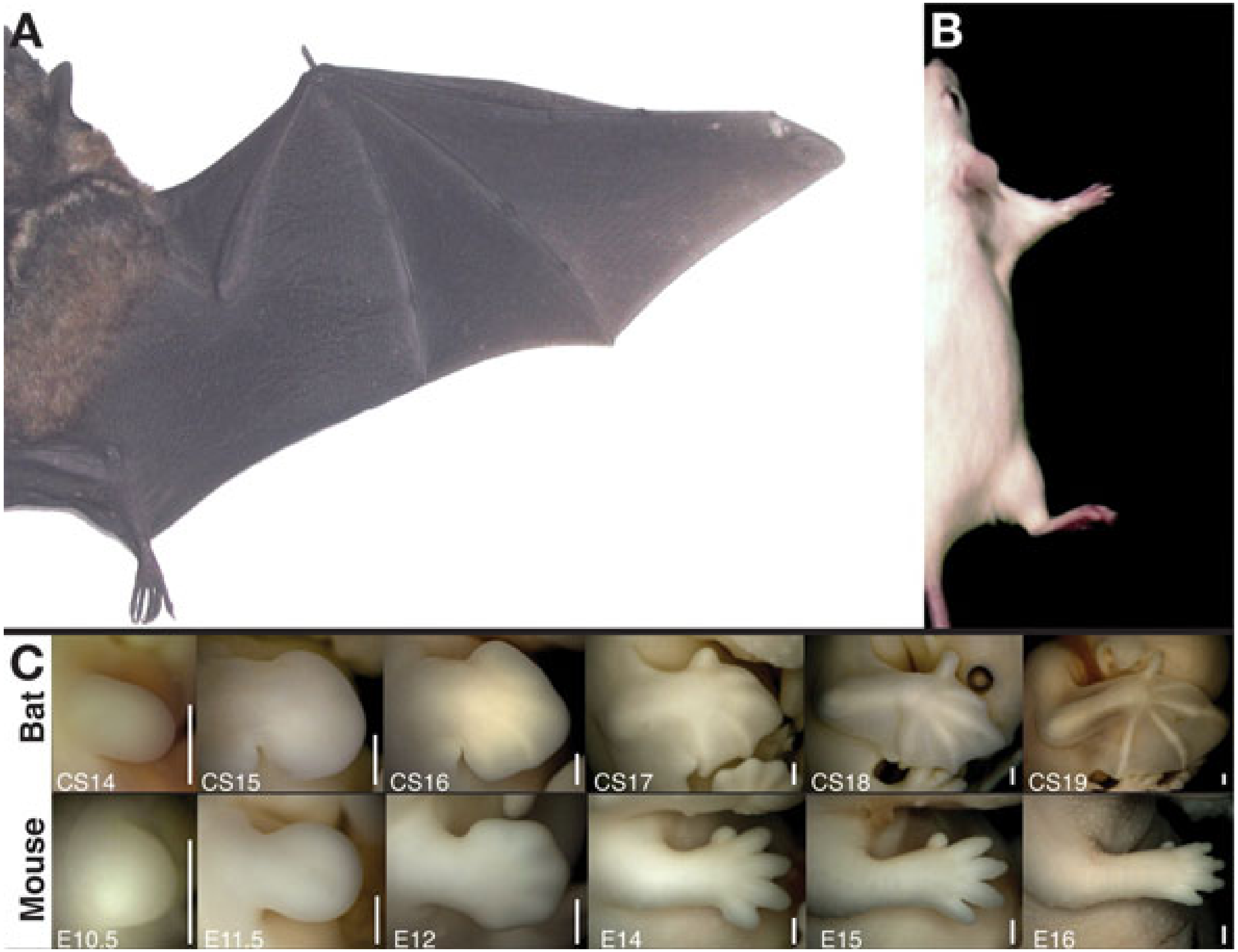


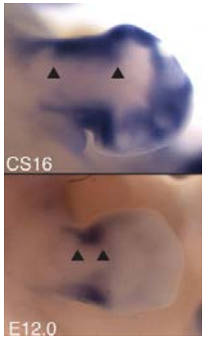
利用此片段調控序列可以強迫*Pitx1*基因在淡水背棘魚的腹部表現，並且在原本沒有腹鰭的魚誘發腹鰭的發育



(Chan et al., ***Science***, 327, 302-305, 2010)

蝙蝠如何演化出翅膀?

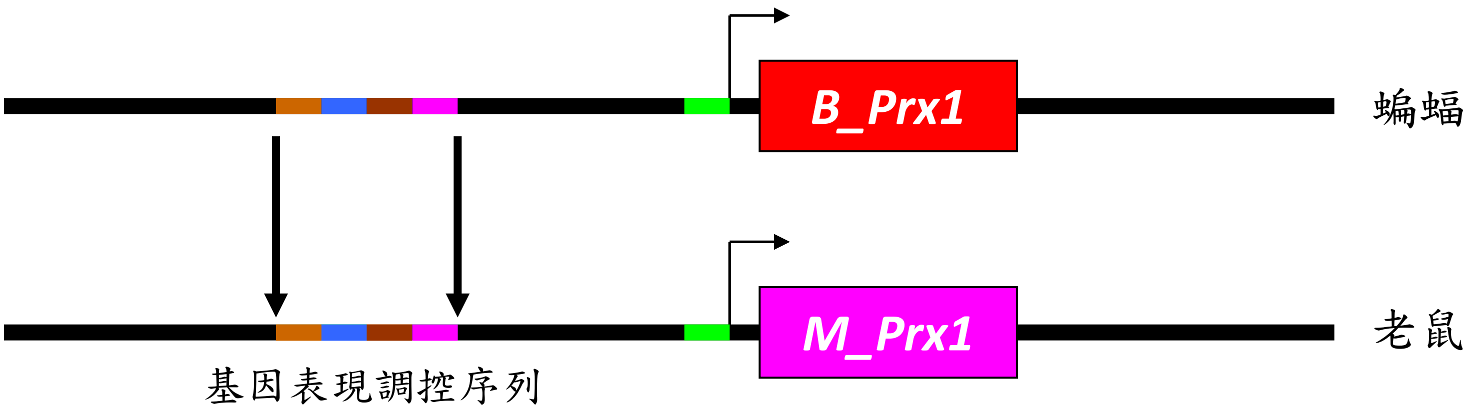


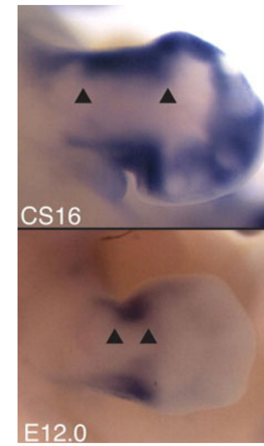


Prx1

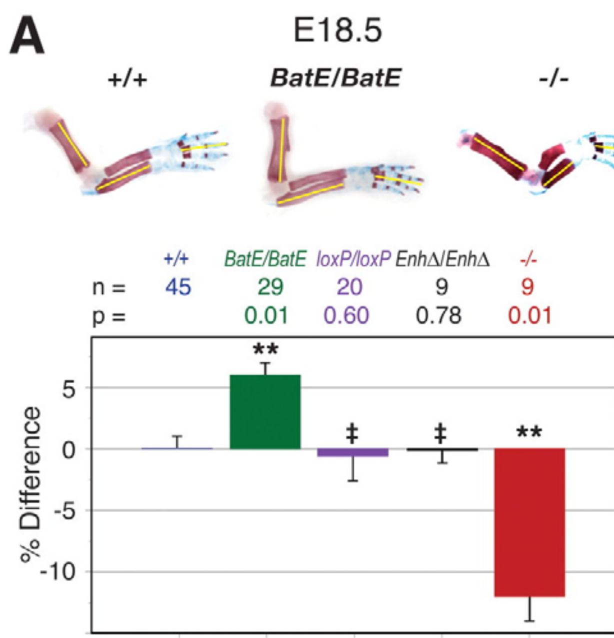
(Cretekos et al., *Genes & Development*, 2008)

蝙蝠如何演化出翅膀?





Prx1

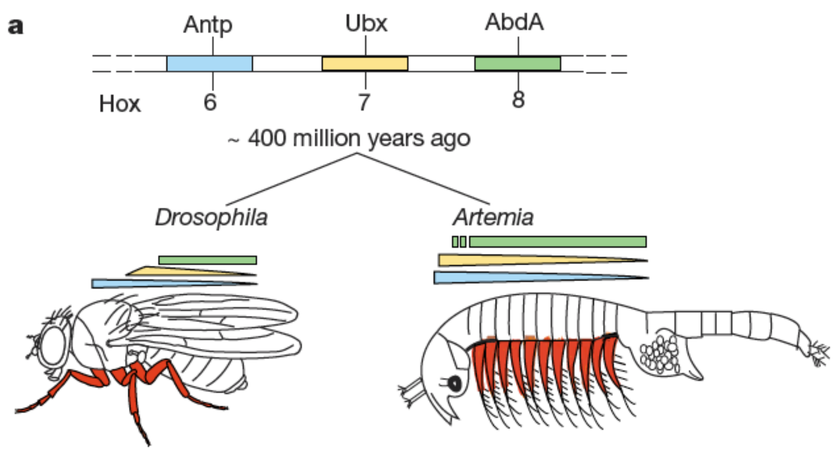


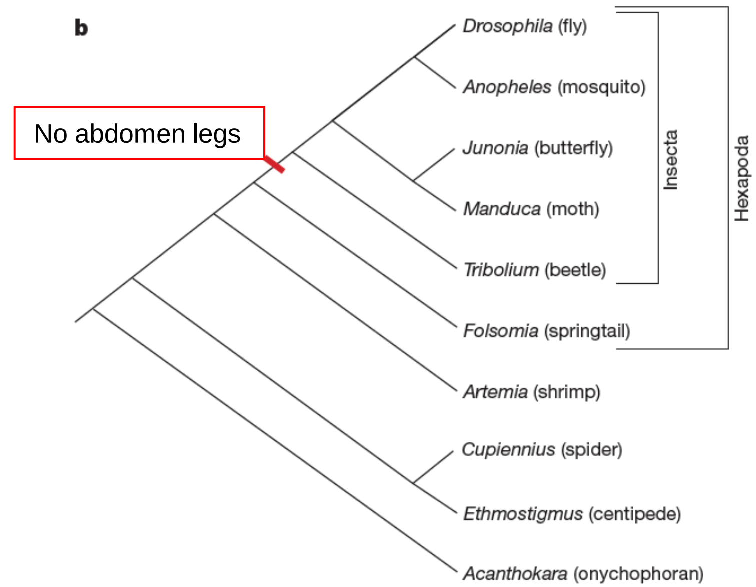
蝙蝠的*Prx1*基因表現調控序列
會造成老鼠前肢增長6%

其他94%的變異要如何解釋?

(Cretekos et al., *Genes & Development*, 2008)

為什麼昆蟲有六隻腳?





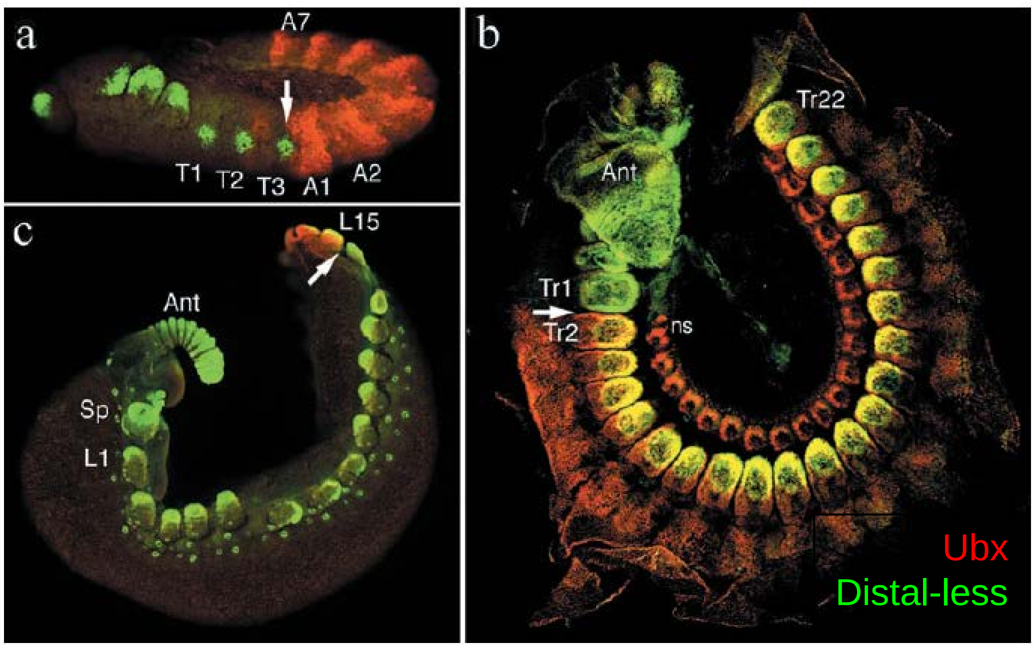
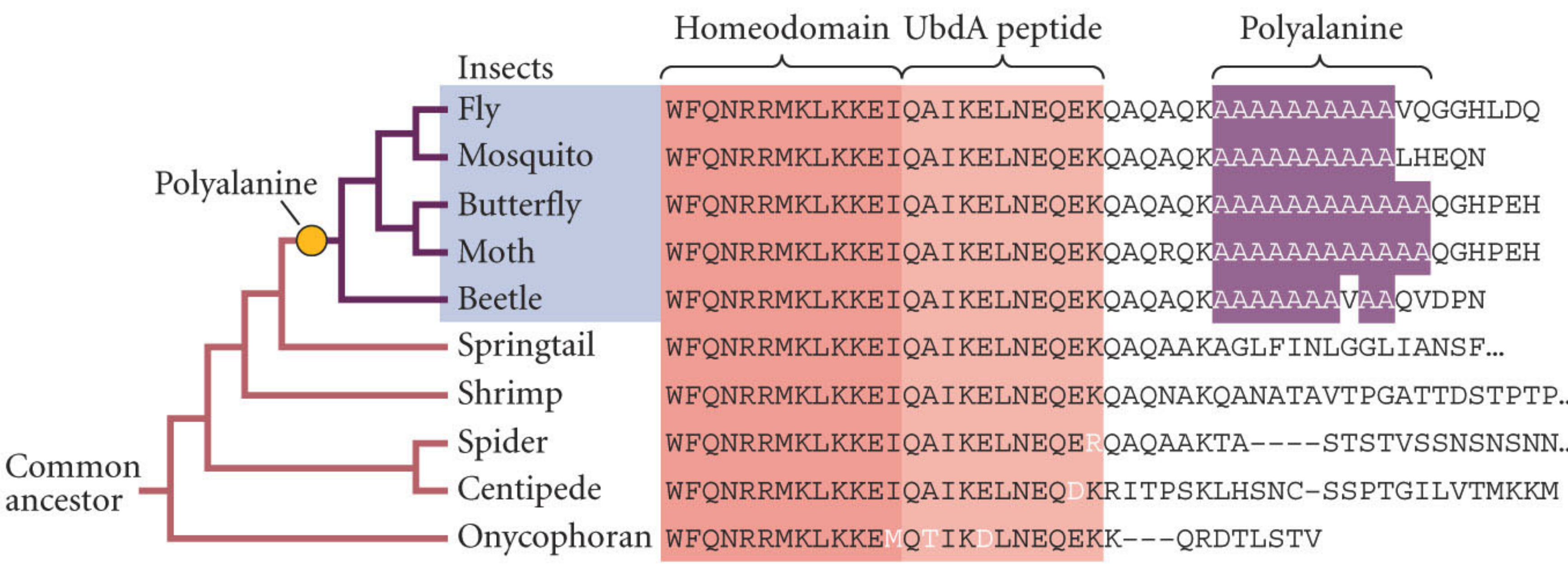


Figure 5.8
Comparison of Ubx and Dll expression in arthropods and onychophora

在大多數節肢動物中，Ubx 無法抑制與腳發育相關的基因*Distal-less*.

但是在昆蟲中Ubx 會抑制*Distal-less*基因的表現，因而昆蟲在後端的腹部體節不會有腳。

昆蟲Ubx蛋白質序列的演化造成基因功能的改變



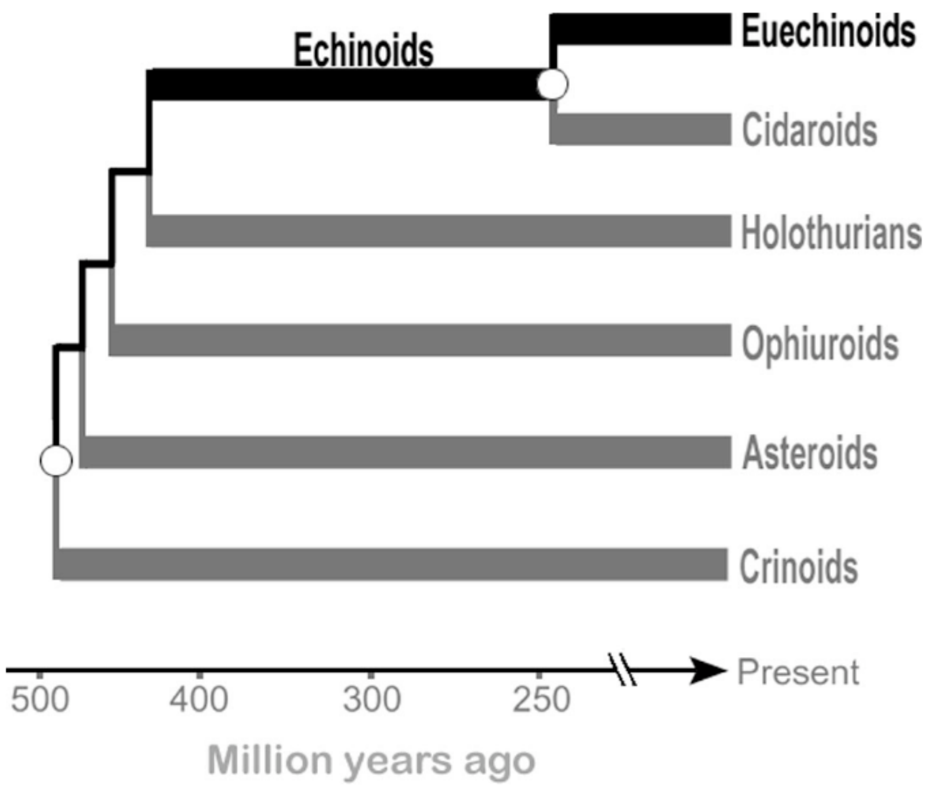
在昆蟲綱中，Ubx蛋白質多了一段poly-alanine序列。這個新演化出來的功能性序列造成昆蟲Ubx蛋白質功能的改變。

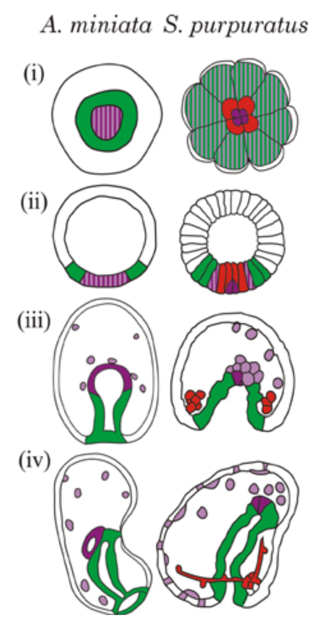
在演化過程中新的構造如何產生？

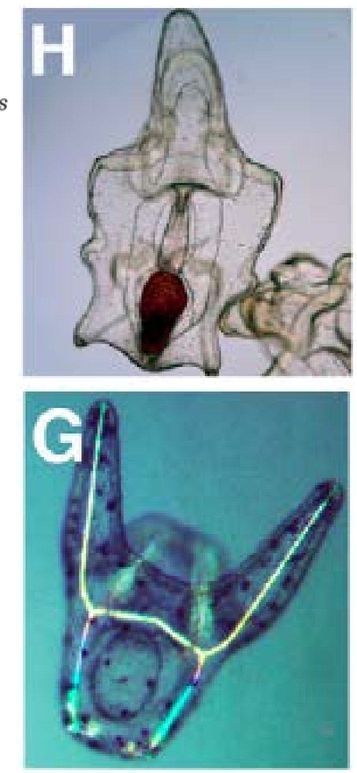
海膽胚胎的骨針怎麼來的？

Of the five echinoderm classes, only the modern sea urchins generate a specified embryonic micromere lineage that ingress before gastrulation and then secretes the biomineral embryonic skeleton.

The skeletogenic micromere lineage is a derived character that appeared after not long after 250 mya.



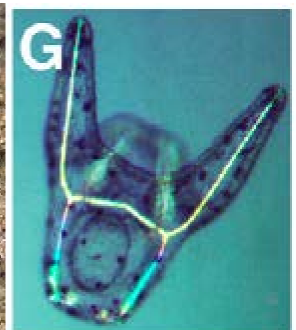




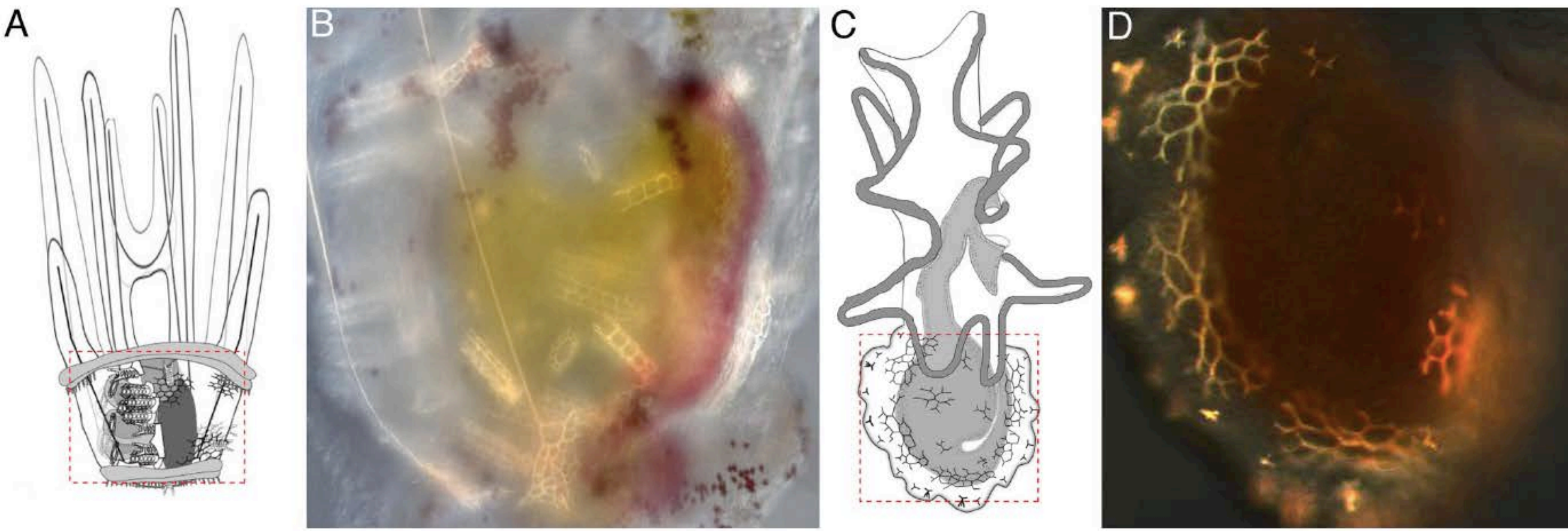
Gao & Davidson, 2008
Hinman et al., 2003

Adult skeletogenesis in sea urchin and sea star larvae

Sea urchin



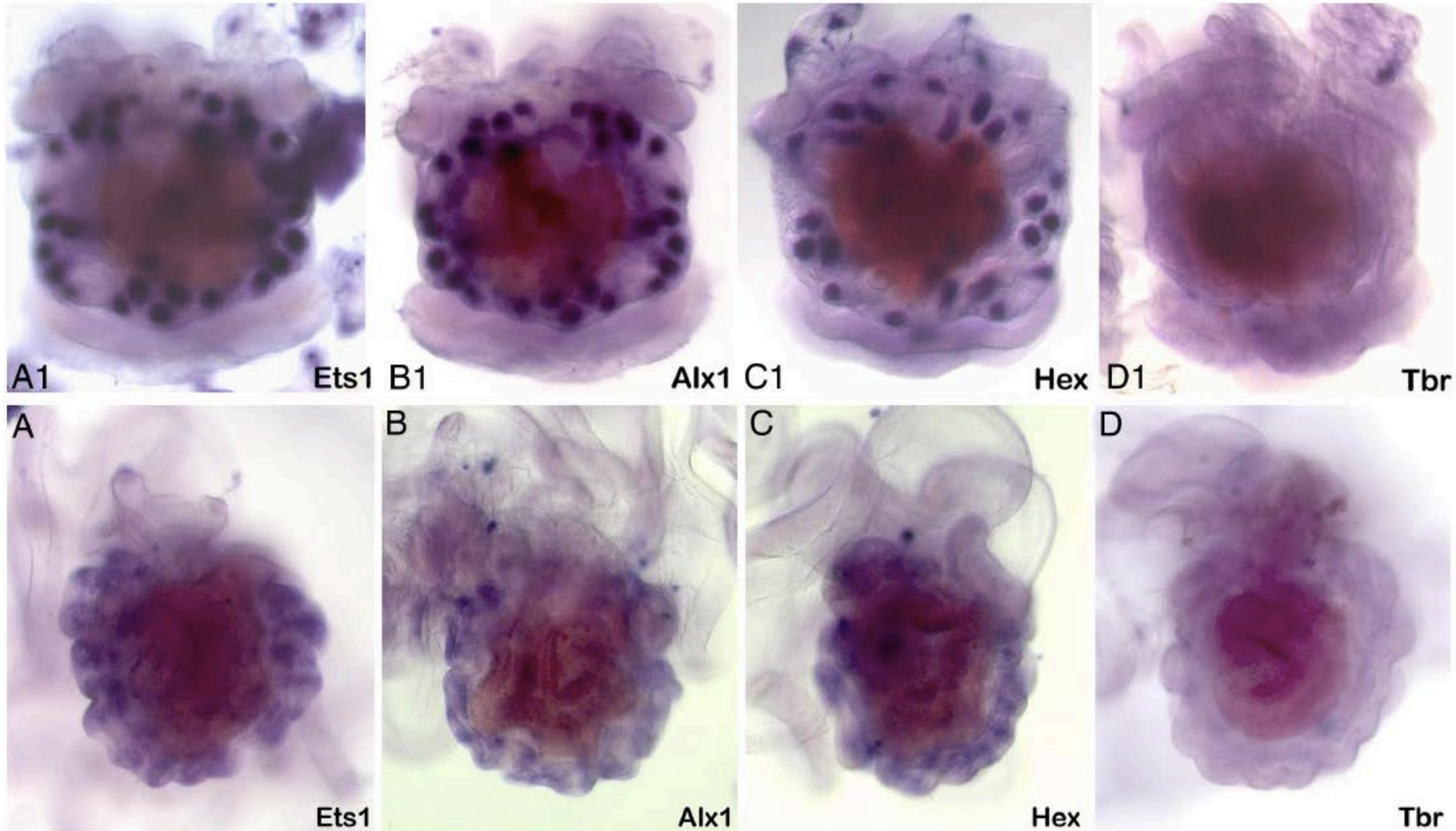
Starfish



Gao & Davidson, 2008

Sea urchin larvae

Sea star larvae

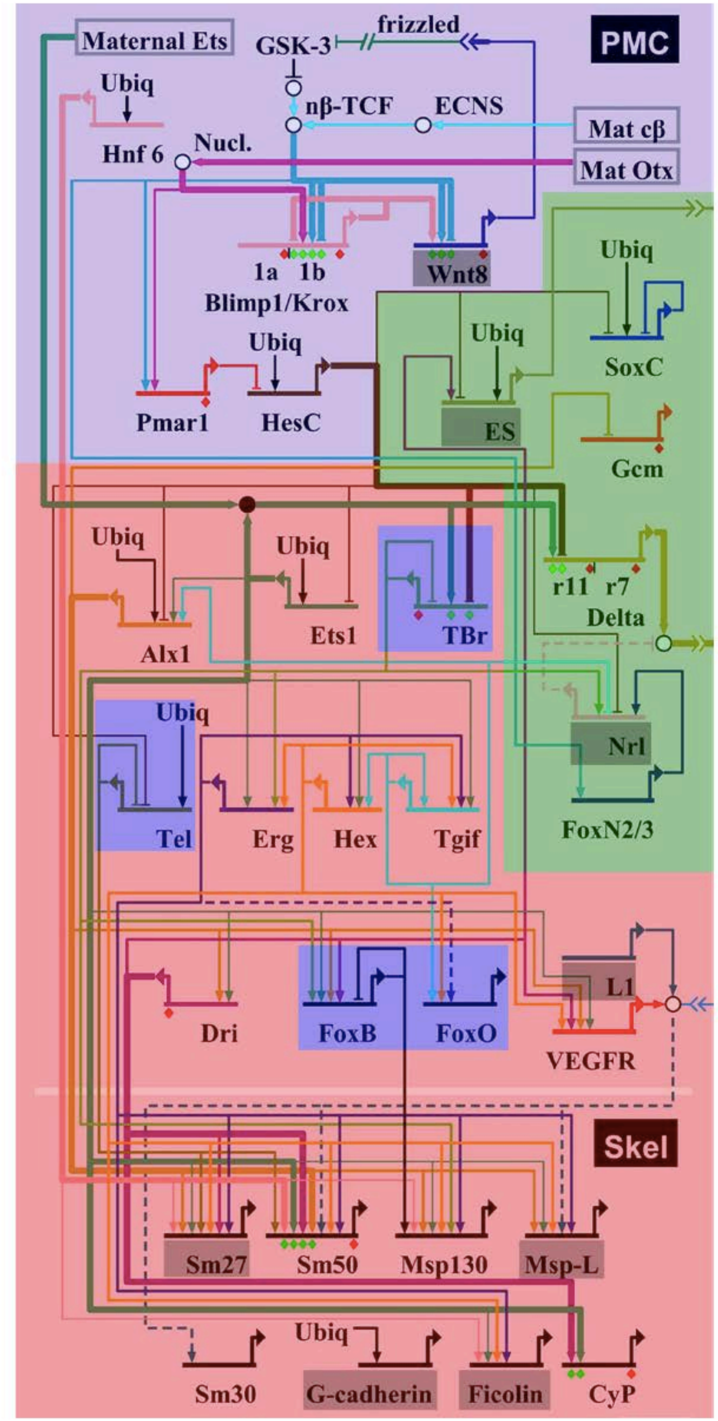


Gao & Davidson, 2008

Many genes used in the biomineralization of the embryo skeleton are also used to make the similar biomineral of the spines and test plates of the adult body

On one side most of the regulatory genes are used in both, and on the other side of which the regulatory apparatus is entirely micromere-specific.

• Genes expressed in juvenile skeletogenic centers and micromere lineage
• Individual cooptions



Gao & Davidson, 2008, *PNAS*

PNAS | April 22, 2008 | vol. 105 | no. 16 | 6091–6096

Transfer of a large gene regulatory apparatus to a new developmental address in echinoid evolution

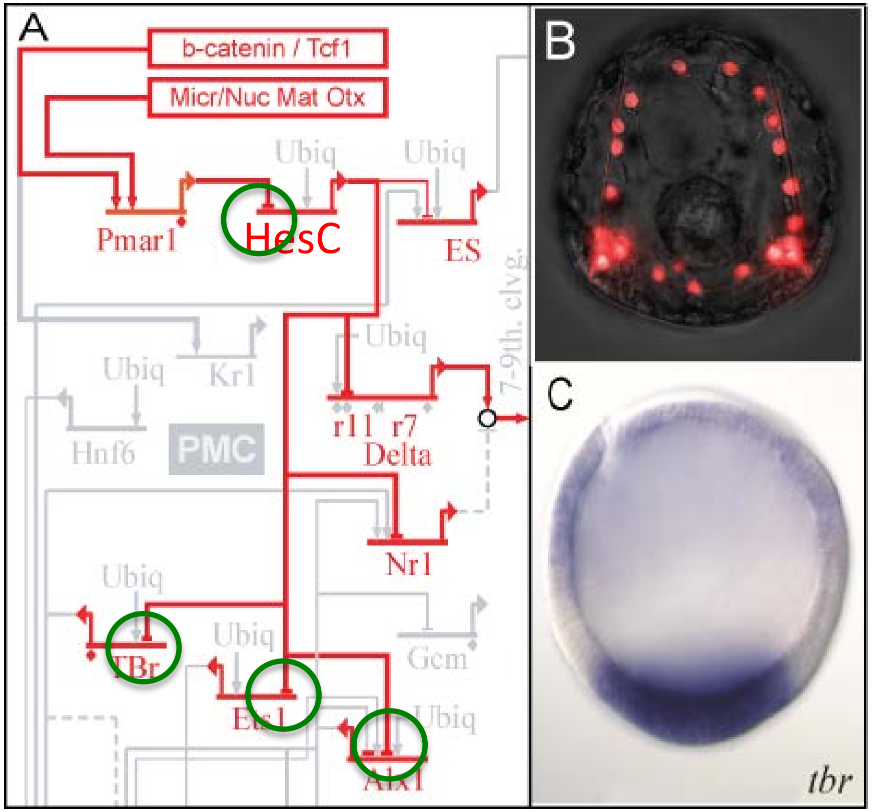
Feng Gao and Eric H. Davidson*

- Pleisiomorphic state is adult skeleton only

- Echinoid embryo skeleton appeared since Permian-Triassic extinction since it is only euechinoid, as did echinoid skeletogenic lineage

- Echinoid micromeres have Pmar1 system used for other things (ex. Delta)

- Minimun path to steal adult skeletogenic pathway:
  - Put HesC sites in CRM of Ets, Alx1, Tbr; put HesC under Pmar1 control

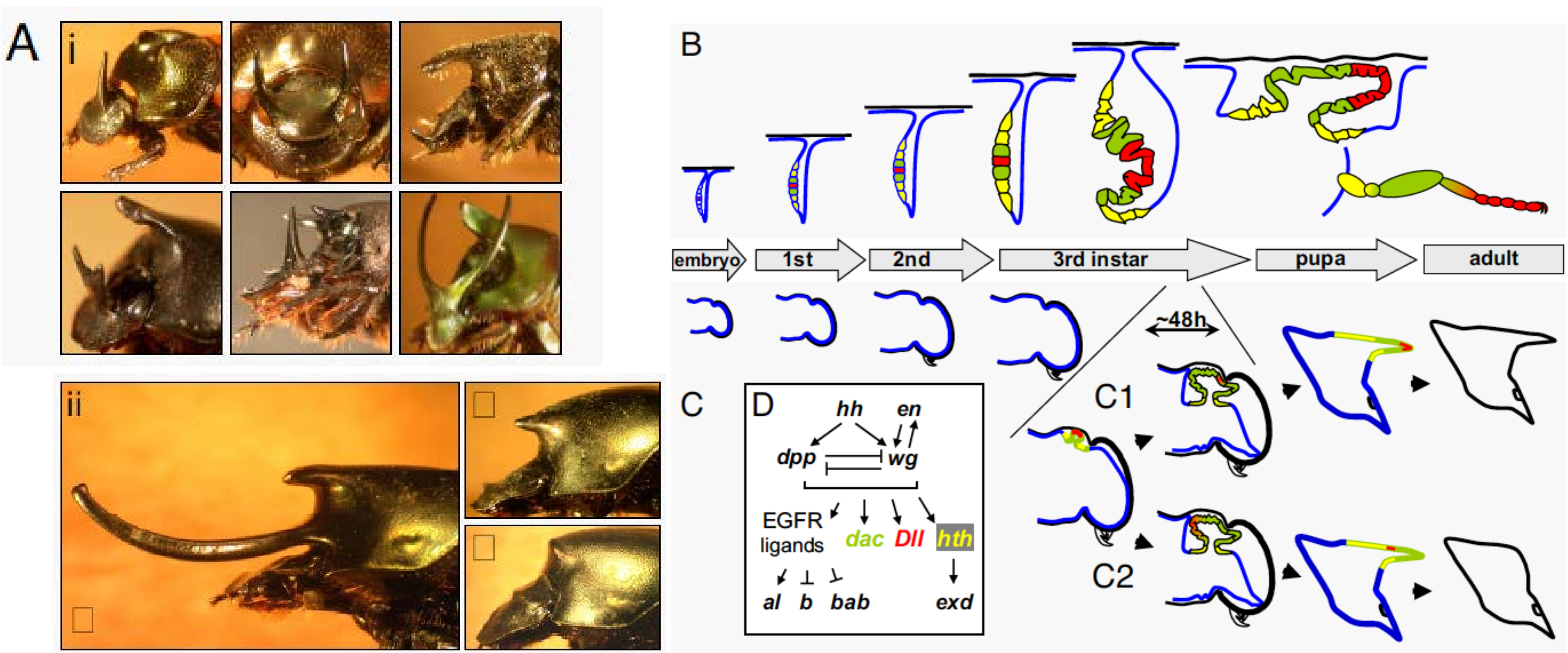


獨角仙的犄角怎麼來的？

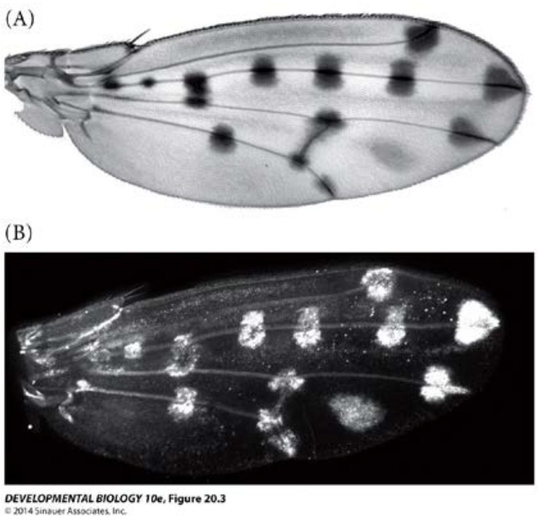
8992–8997 | PNAS | June 2, 2009 | vol. 106 | no. 22

Differential recruitment of limb patterning genes during development and diversification of beetle horns

Armin P. Moczek[1] and Debra J. Rose



果蠅翅膀上的斑點怎麼來的？



Yellow protein – promote black melanin formation

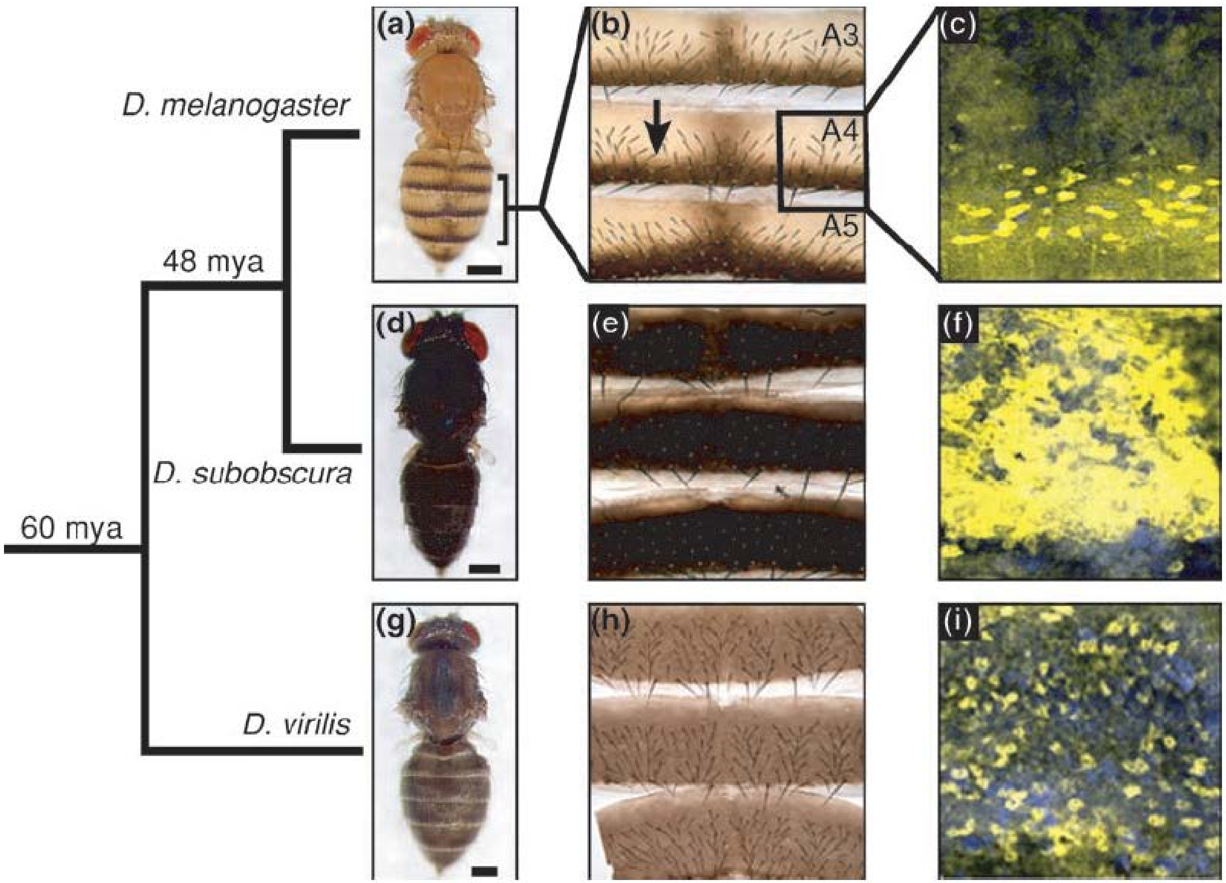


Figure 7.5
Evolution of body color and *yellow* gene regulation in *Drosophila* species

Co-option of pigmentation genes into existing wing modules

甲蟲的鞘翅怎麼來的？

Elytra – the hardened forewings of beetles

In *Drosophila*, *Apterous* gene is expressed in the wing disc.
In beetles, Apterous activates exoskeleton genes in the forewing.

Recruitment of one module (exoskeletal development) into another (forewing development)

(A)

(B)

***DEVELOPMENTAL BIOLOGY 10e*, Figure 20.4**

在演化過程中新構造的產生是利用現有的發育機制修改後再利用

Co-option of one into another

New structure is formed by the **recruitment** of existing modules

動物的發育機制與演化

祖先的發育機制 → 祖先的型態

↓ ↓

發育機制的變化 → 型態的改變

演化發育生物學 (Evolutionary Developmental Biology, EvoDevo)：

結合演化生物學與發育生物學，從發育機制的角度來探討演化的問題