

# Princípios gerais do desenvolvimento: regulação génica, especificação celular e diferenciação

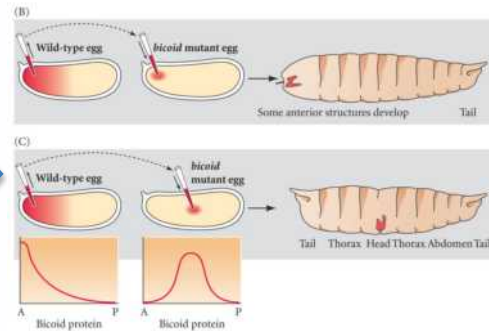
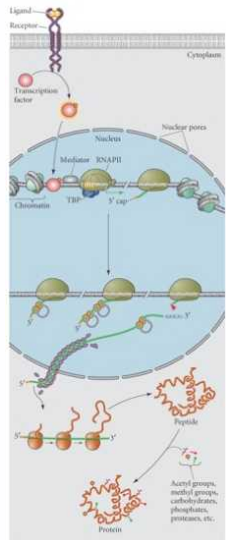


stage 2 Nuclear division Number: 5



# Princípios gerais do desenvolvimento:

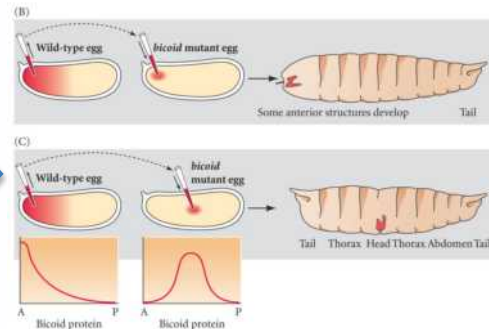
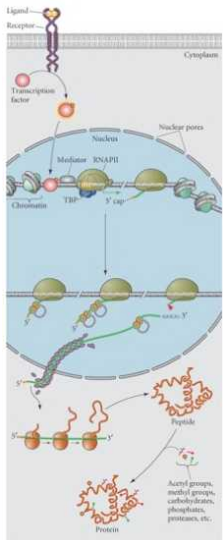
## A. Regulação gênica



## B. Gradientes e morfógenos

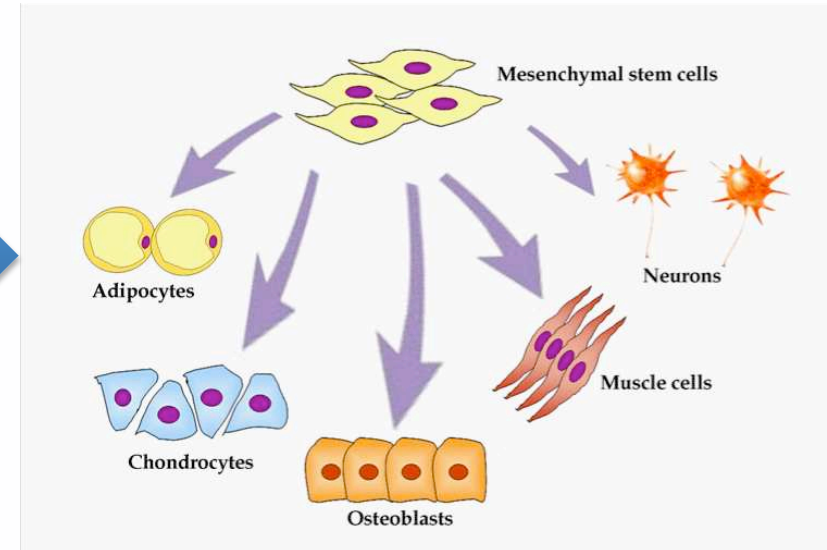
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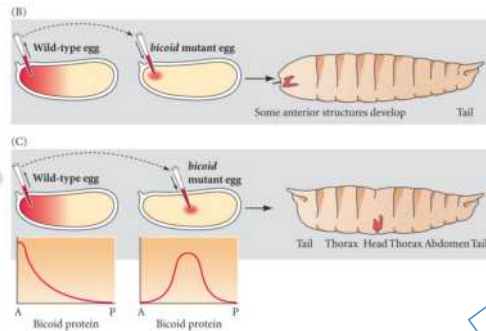
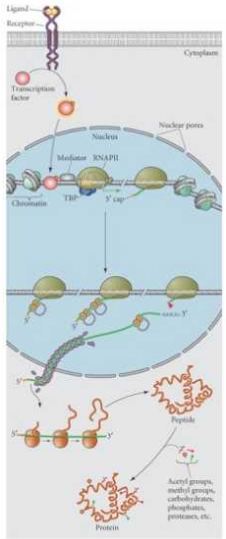
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## C. Especificação e diferenciação celular:



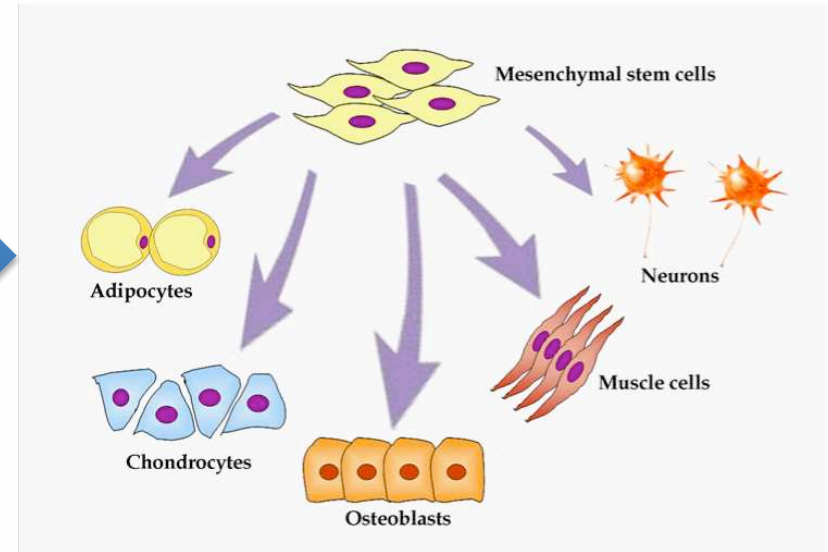
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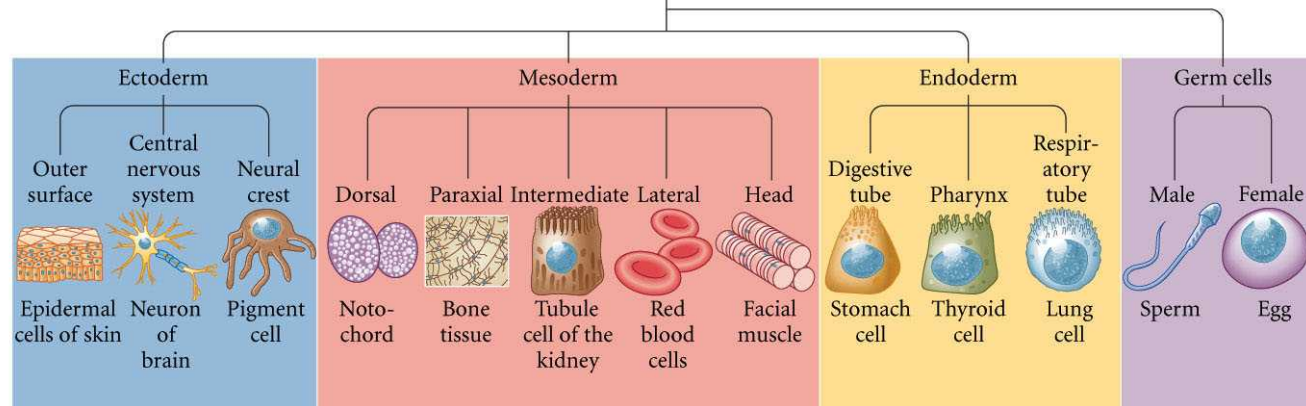
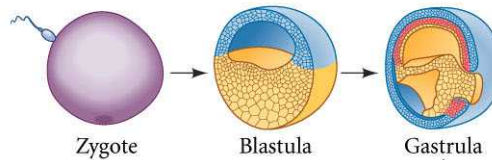
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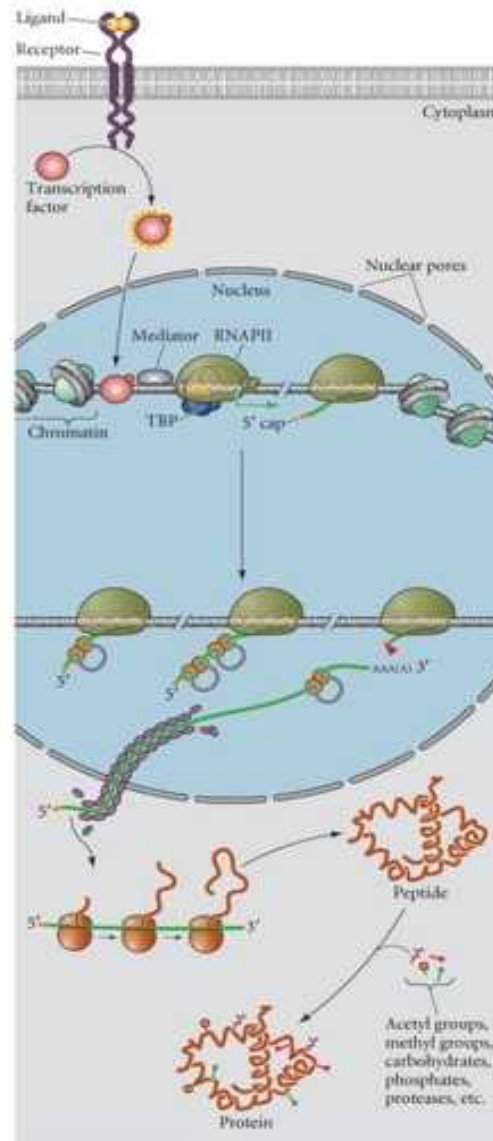
## C. Especificação e diferenciação celular embrionária:

- I. autônomo
- II. condicional
- III. (-syncycial)



# A. Regulação génica: expressão dos genes pode ser regulado em vários níveis

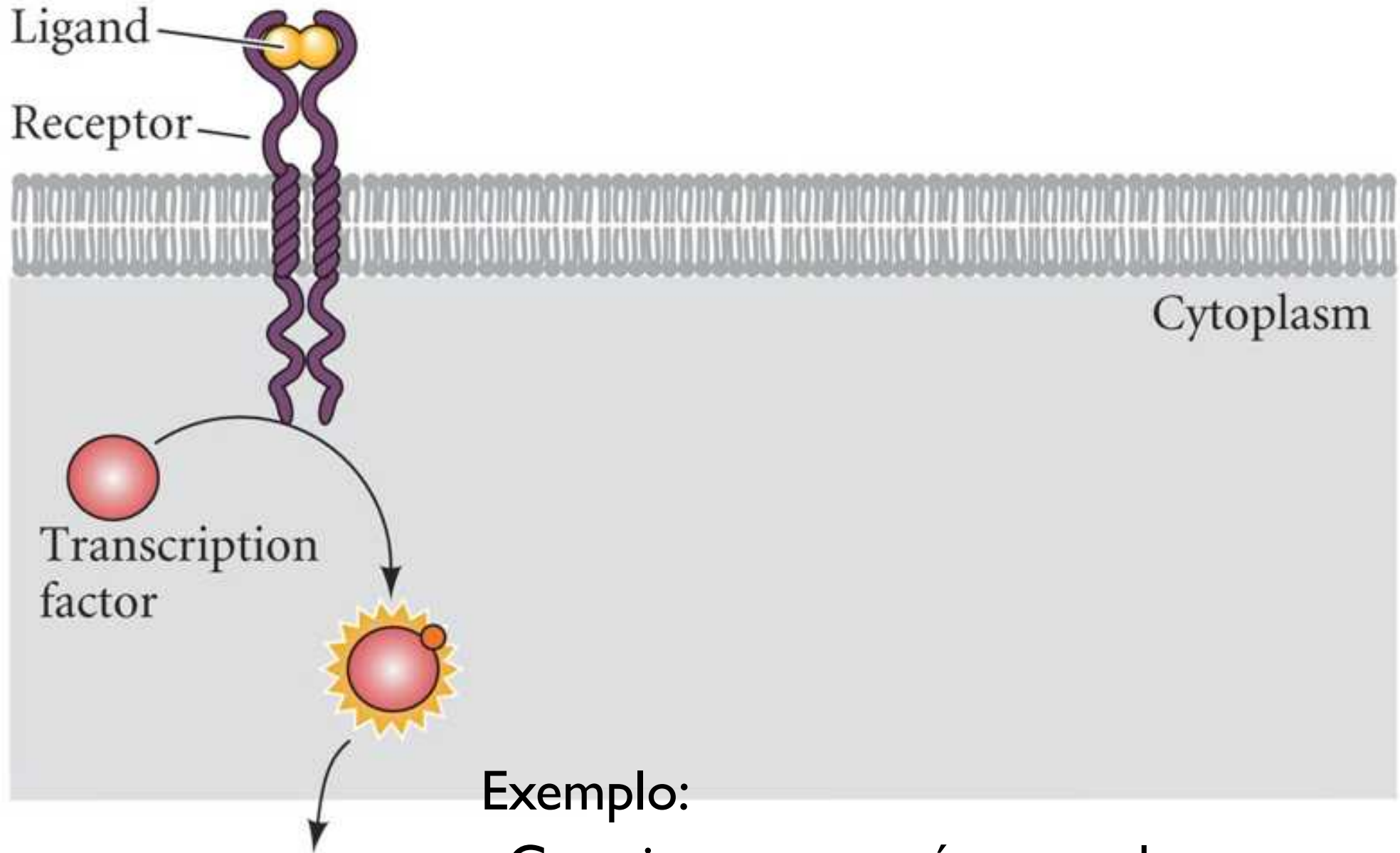
## 2) Transcrição



1) Ambiente extracelular e cascatas de sinalização

3) Tradução

# I) Ambiente extracelular e cascatas de sinalização:





# Crecimiento corpóreo em humanos

## Caso: Nanismo pituitário (Síndrome de Laron ou GHRD)



Rosenbloom et al. 1999

TABLE 1. Clinical features of GHRD

### Growth

- Birth weight-normal; birth length-usually normal<sup>a</sup>
- Severe growth failure, from birth, with growth velocity ½ normal<sup>a</sup>
- Height deviation correlates with (low) serum levels of IGF-I and IGFBP-3<sup>b</sup>
- Delayed bone age, but advanced for height age<sup>a</sup>
- Small (<10th percentile for height) hands or feet (70%)<sup>a</sup>
- Body segment ratios normal for bone age in children, abnormal (reduced upper/lower, arms span) in adults<sup>b</sup>

### Craniofacial characteristics

- Sparse hair before age 7 (70%); frontal temporal hairline recession all ages<sup>a</sup>
- Prominent forehead
- Head size more normal than stature with impression of large head<sup>b</sup>

### Hypoplastic nasal bridge, shallow orbits

- Decreased vertical dimension of face<sup>a</sup>
- “Setting sun sign” under 10 yr of age (25%)<sup>a</sup>
- Blue scleras<sup>b</sup>
- Prolonged retention of primary dentition with decay; normal, crowded permanent teeth
- Sculpted chin<sup>b</sup>
- Unilateral ptosis, facial asymmetry (15%)<sup>b</sup>

### Musculoskeletal/body composition

- Hypomuscularity with delay in walking (70%)<sup>a</sup>
- Hip dysplasia: avascular necrosis of femoral head (25%)<sup>a</sup>
- High pitched voices in all children, 90% adults<sup>a</sup>

### Thin, prematurely aged skin

- Limited elbow extensibility (acquired; 85% after age 5 yr)<sup>b</sup>
- Children underweight to normal for height, most adults overweight for height; markedly decreased ratio of lean mass to fat mass, compared to normal, at all ages<sup>b</sup>
- Osteopenia<sup>a</sup>

### Metabolic

#### Hypoglycemia (fasting)

- Increased cholesterol and LDL-C<sup>b</sup>
- Decreased sweating

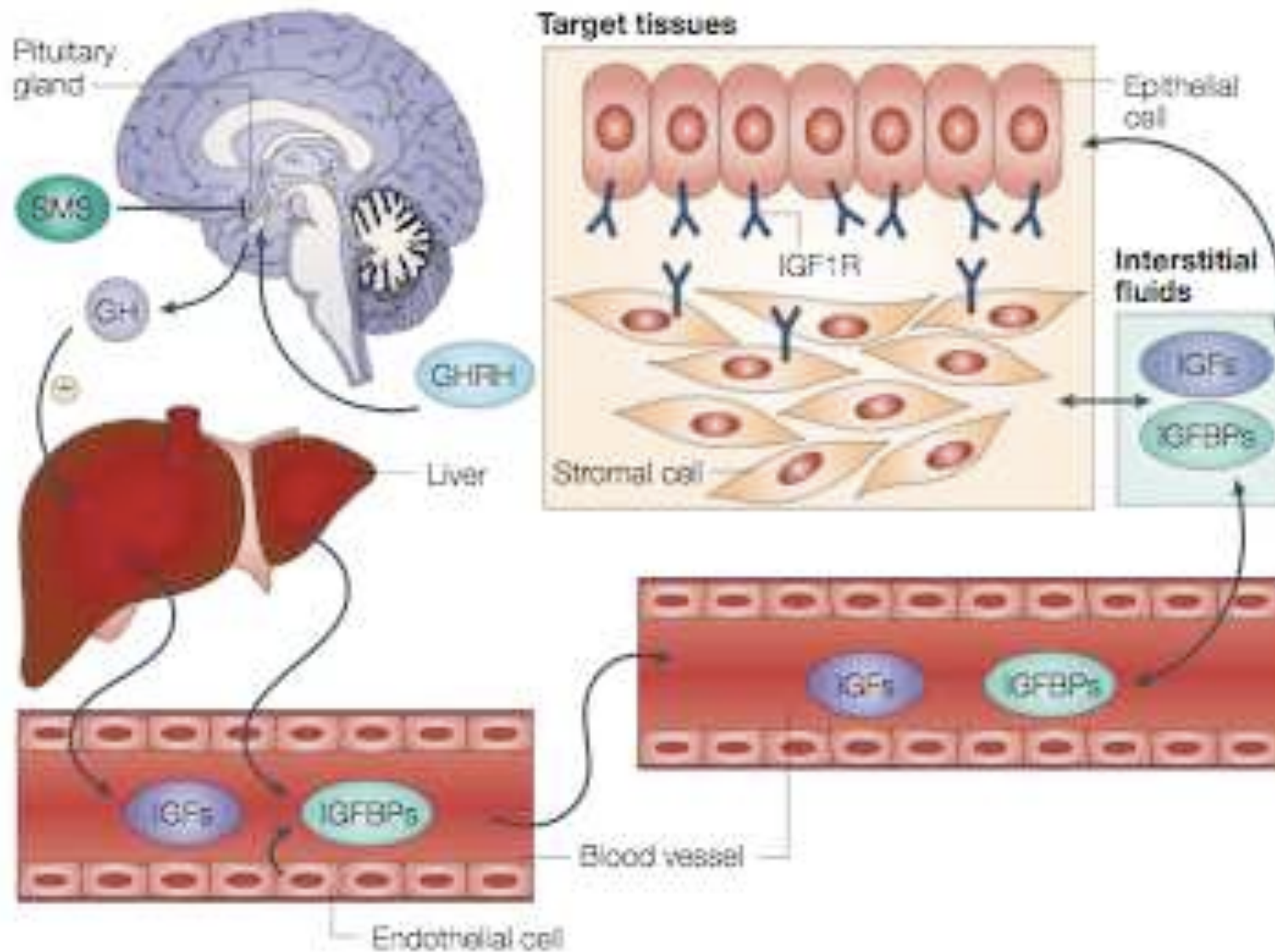
### Sexual development

- Small penis in childhood; normal genital growth with adolescence
- Delayed puberty (50%) in both sexes<sup>a</sup>
- Normal reproductive function<sup>a</sup>

<sup>a</sup> Observations expanded, modified, or quantified in the Ecuadorian cohort.

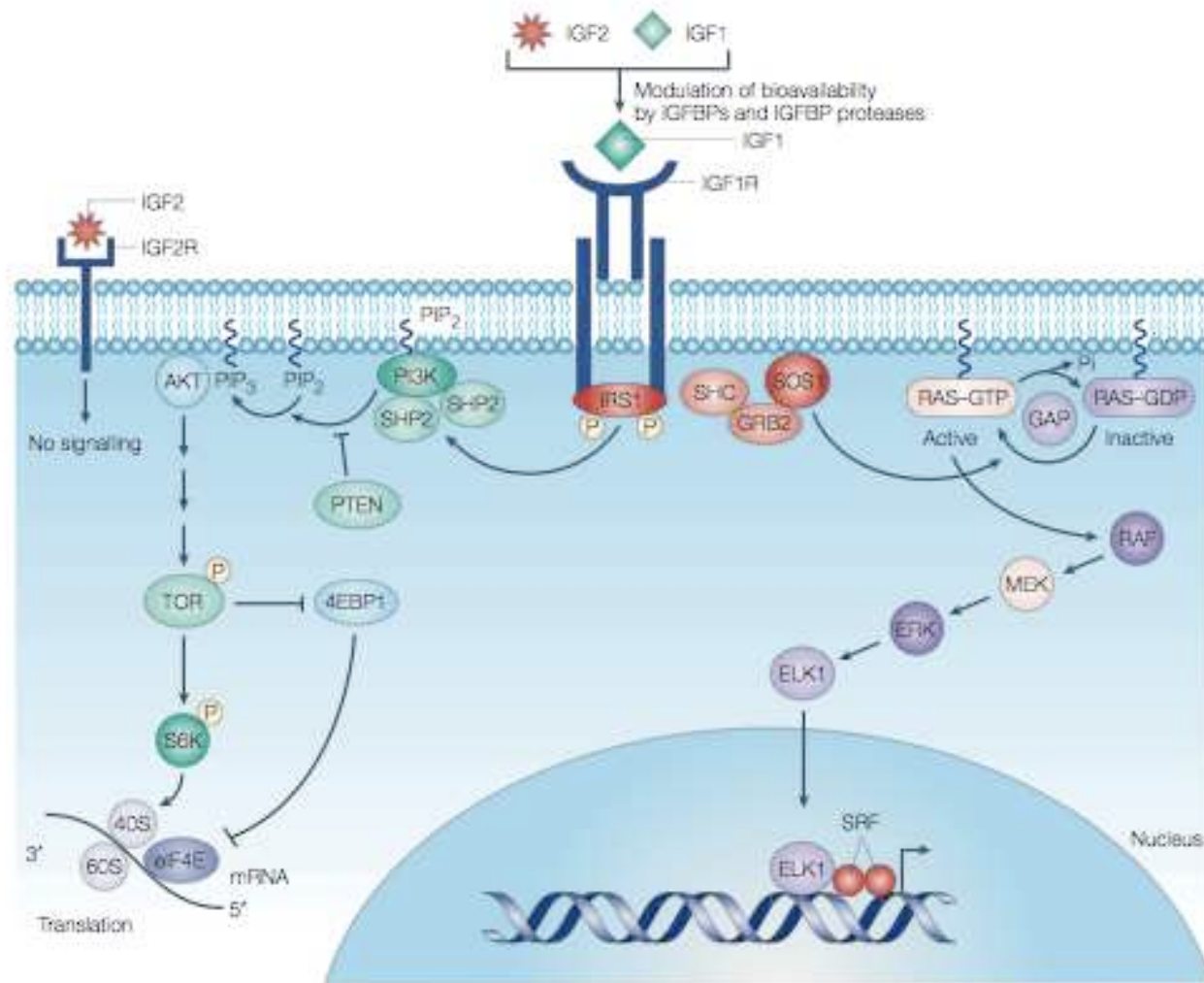
<sup>b</sup> New observations in the Ecuadorian cohort.

# Caso: Nanismo pituitário (Síndrome de Laron ó GHRD)



Pollak et al. 2004





Pollak et al. 2004

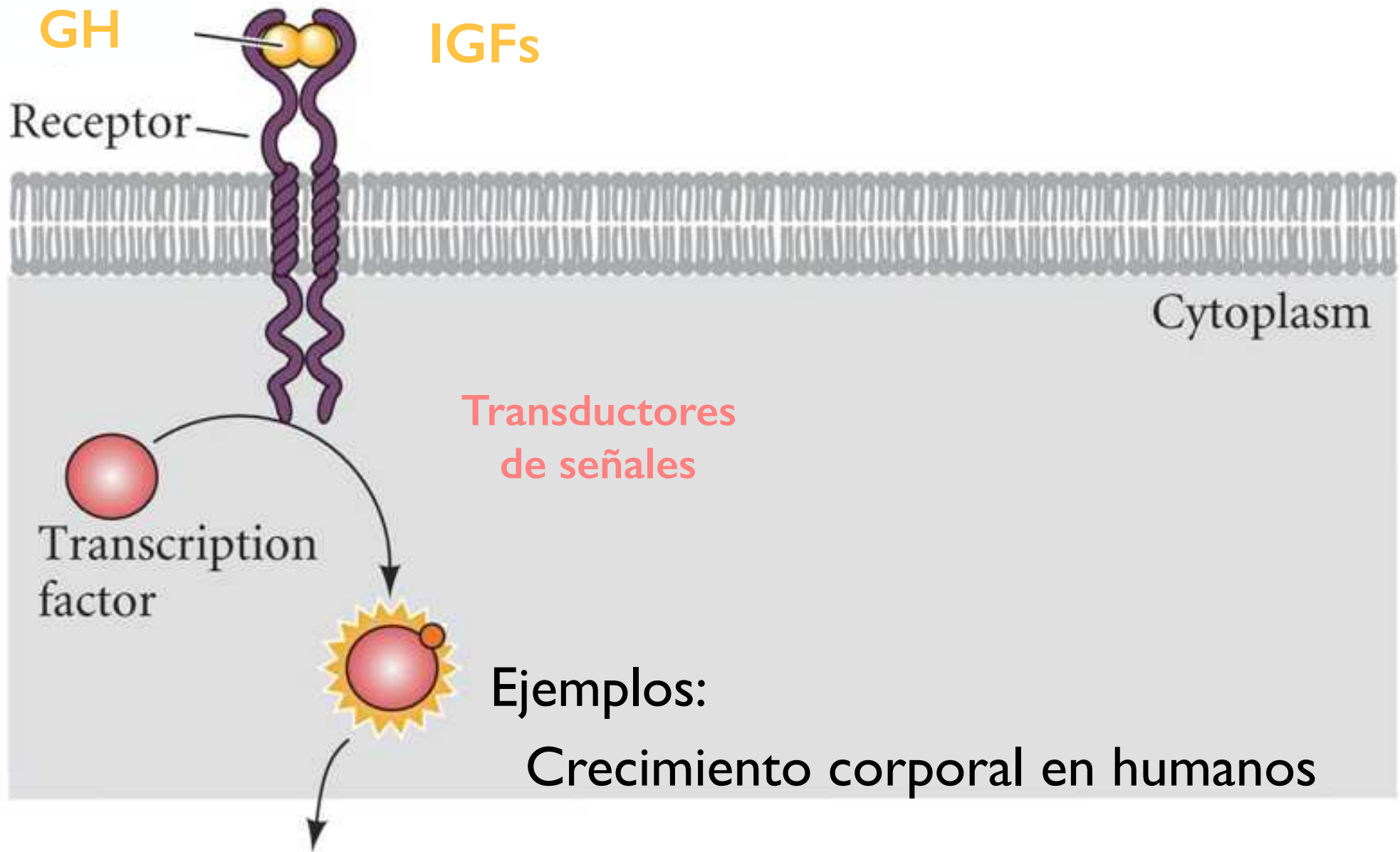
Se você fosse o médico,  
o qual tratamento você  
aplicaria à seus  
pacientes?

# Tratamiento con IGF-I



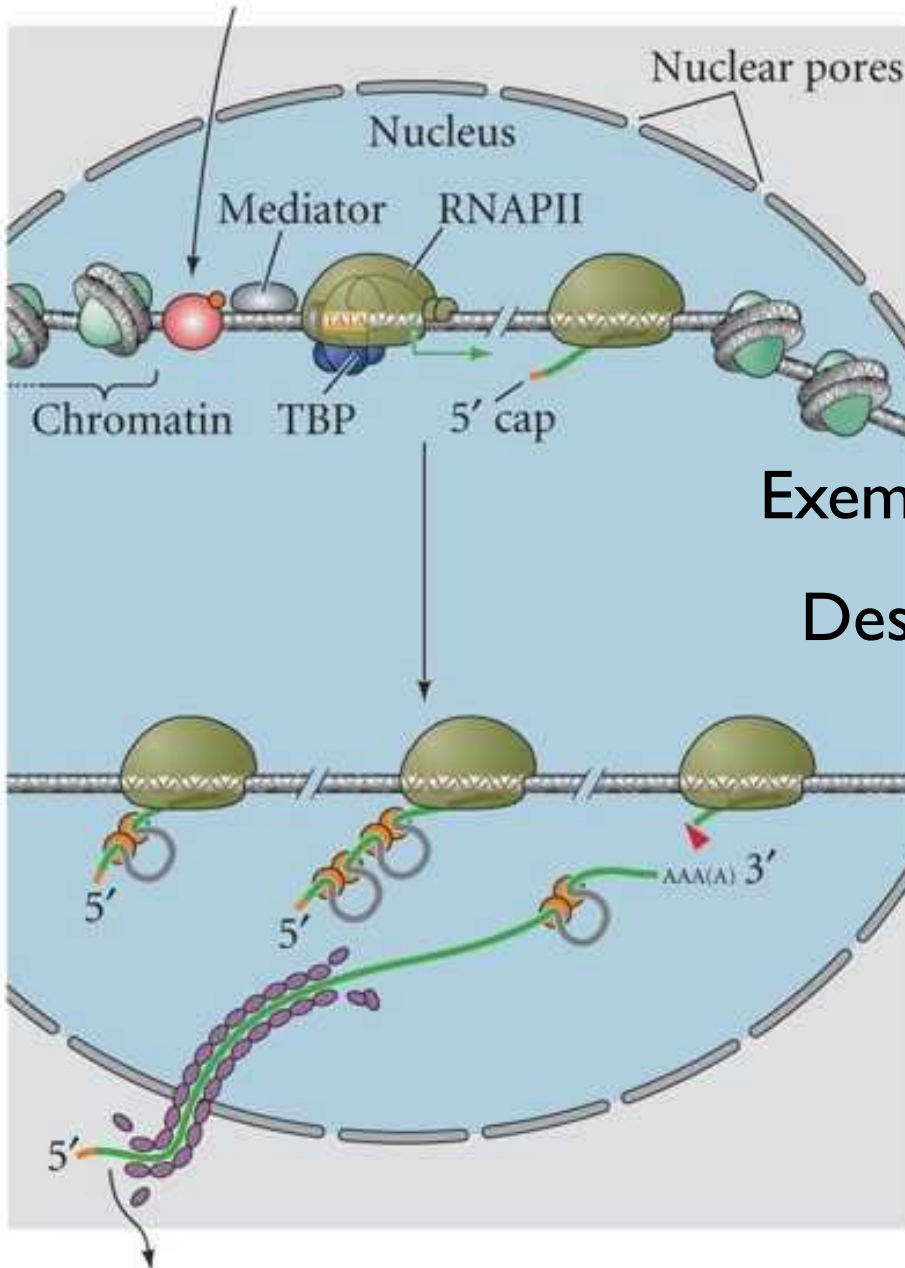
Paciente de 18 años, seis meses  
después de tratamiento

# I) Resumo sinalização:





## 2) Transcrição

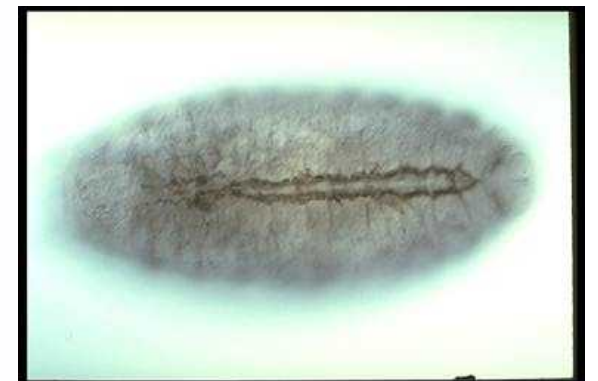


Exemplo:

Desenvolvimento do coração

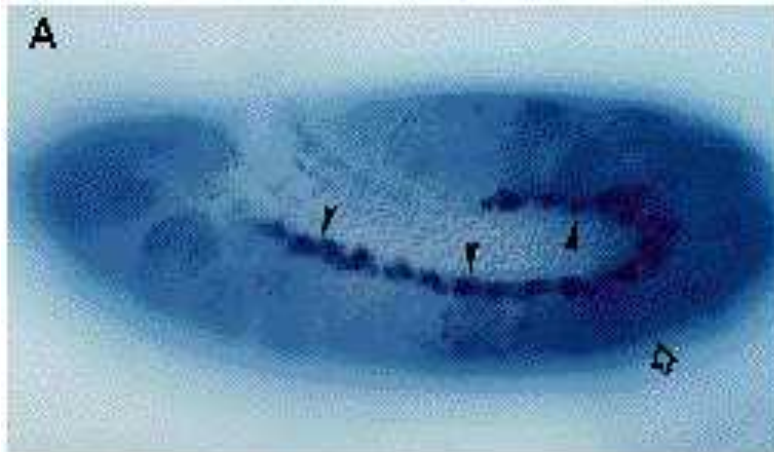


*Drosophila:*

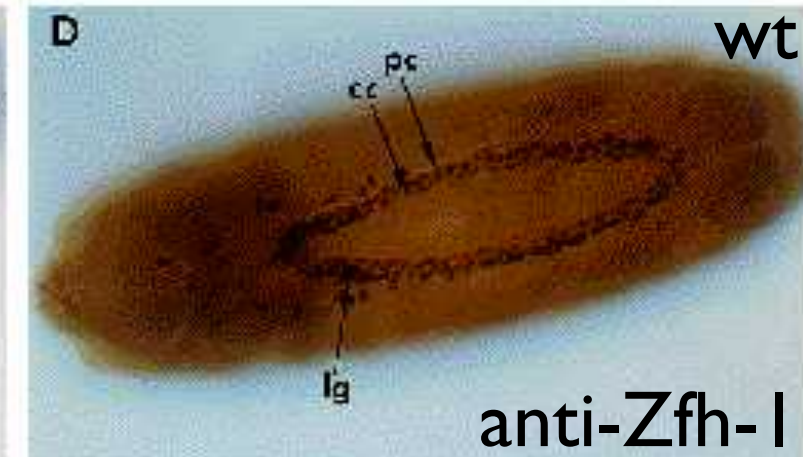
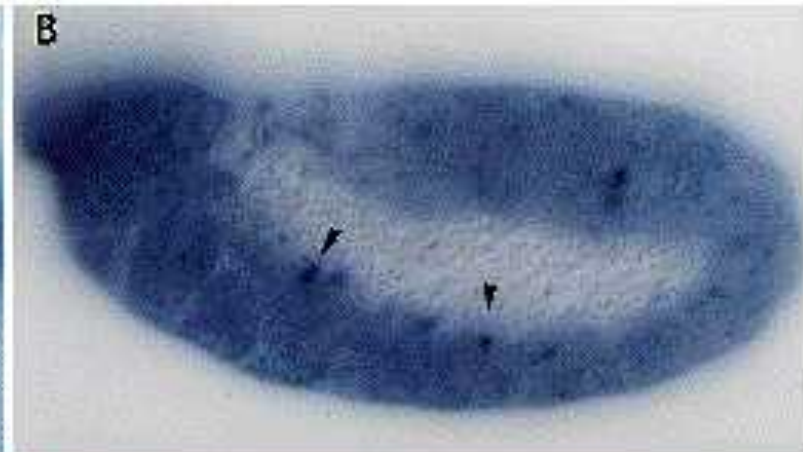


# *tinman* (*tin* RNA)

wt



*tin*EC40

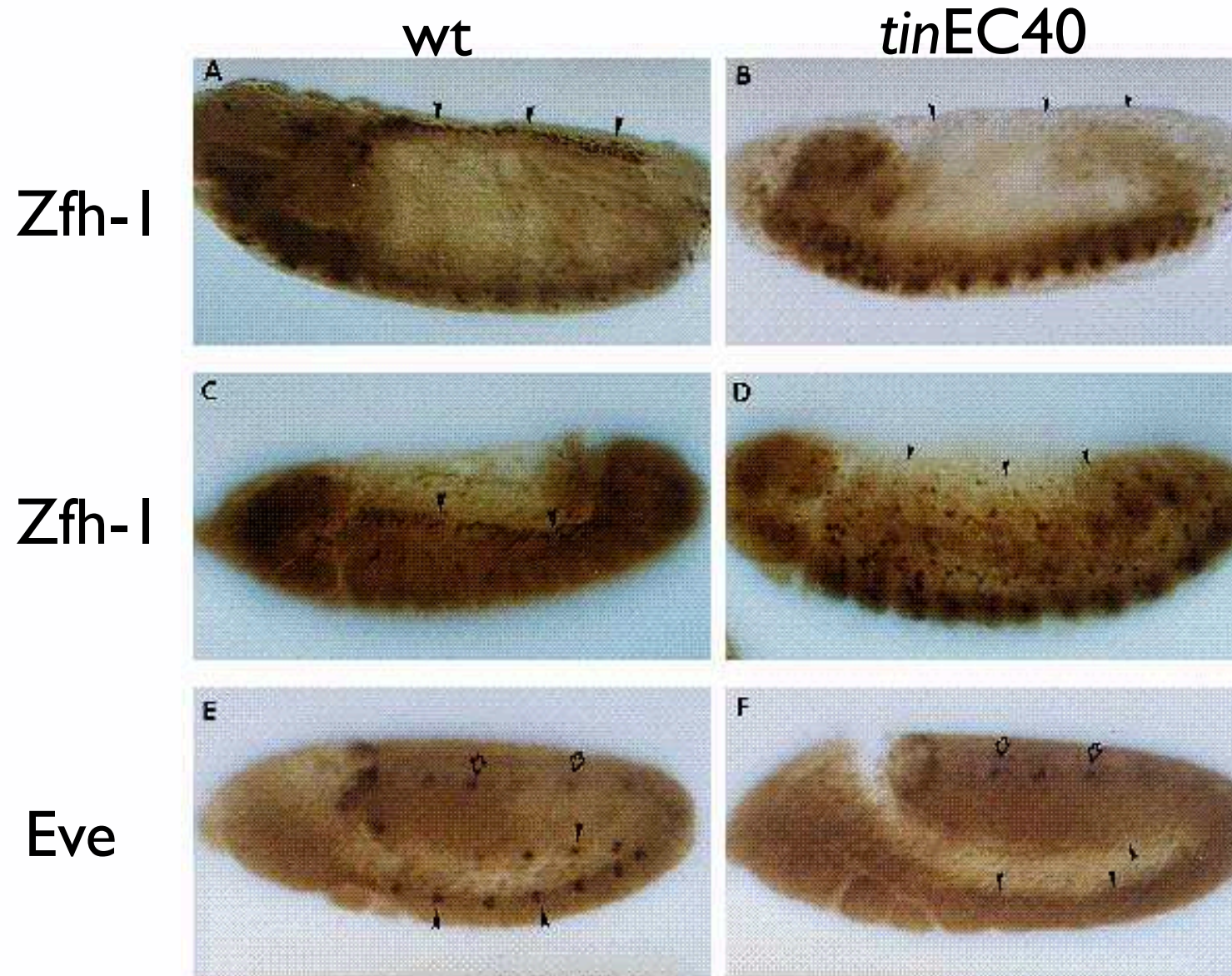


anti-Zfh-1

Bodmer 1993

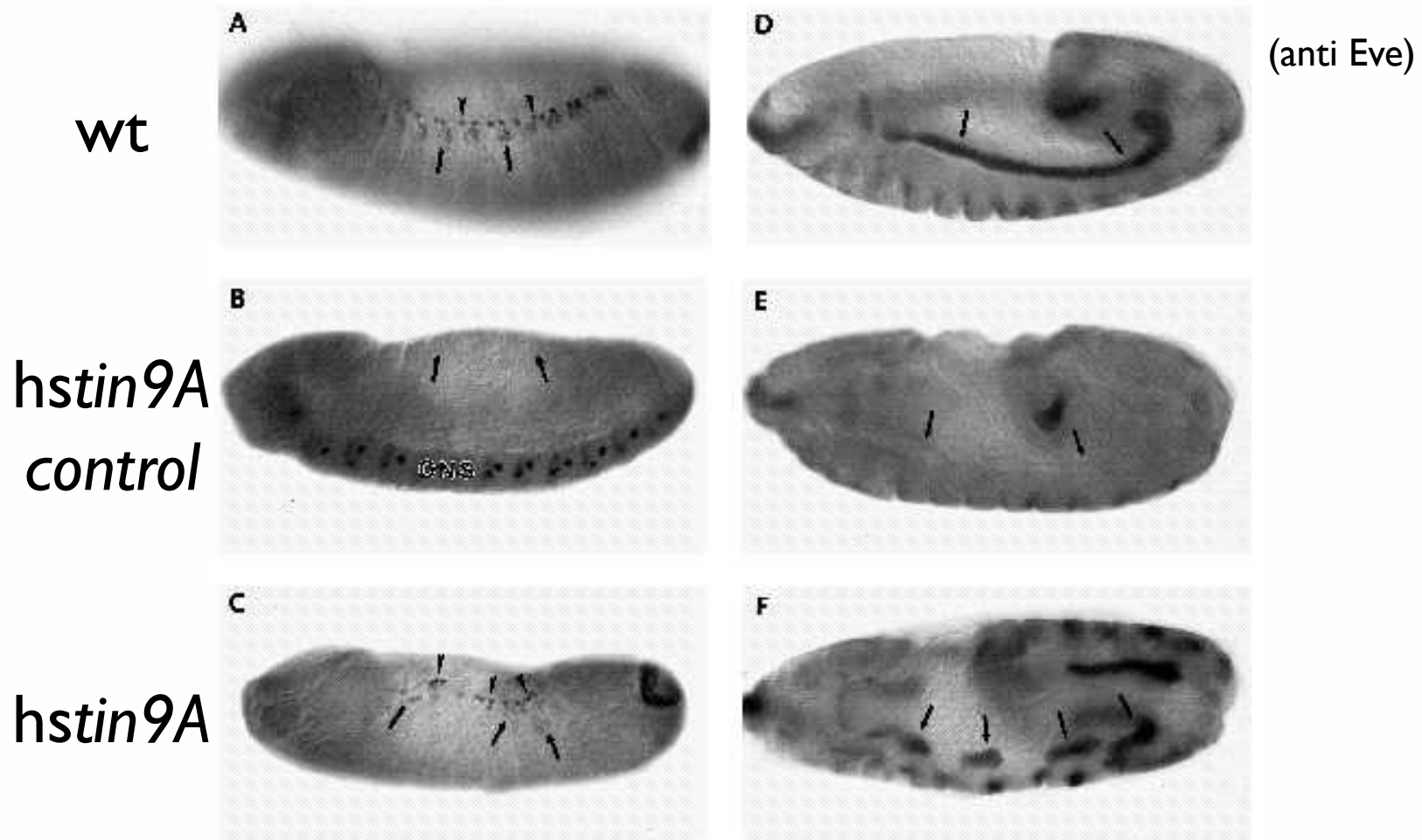


# desenvolvimento do coração

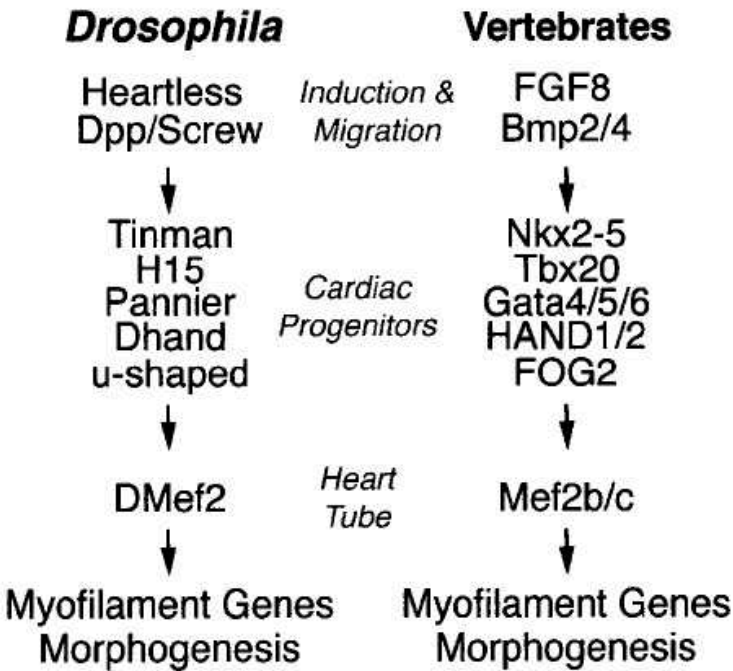
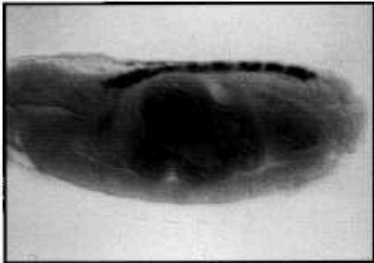




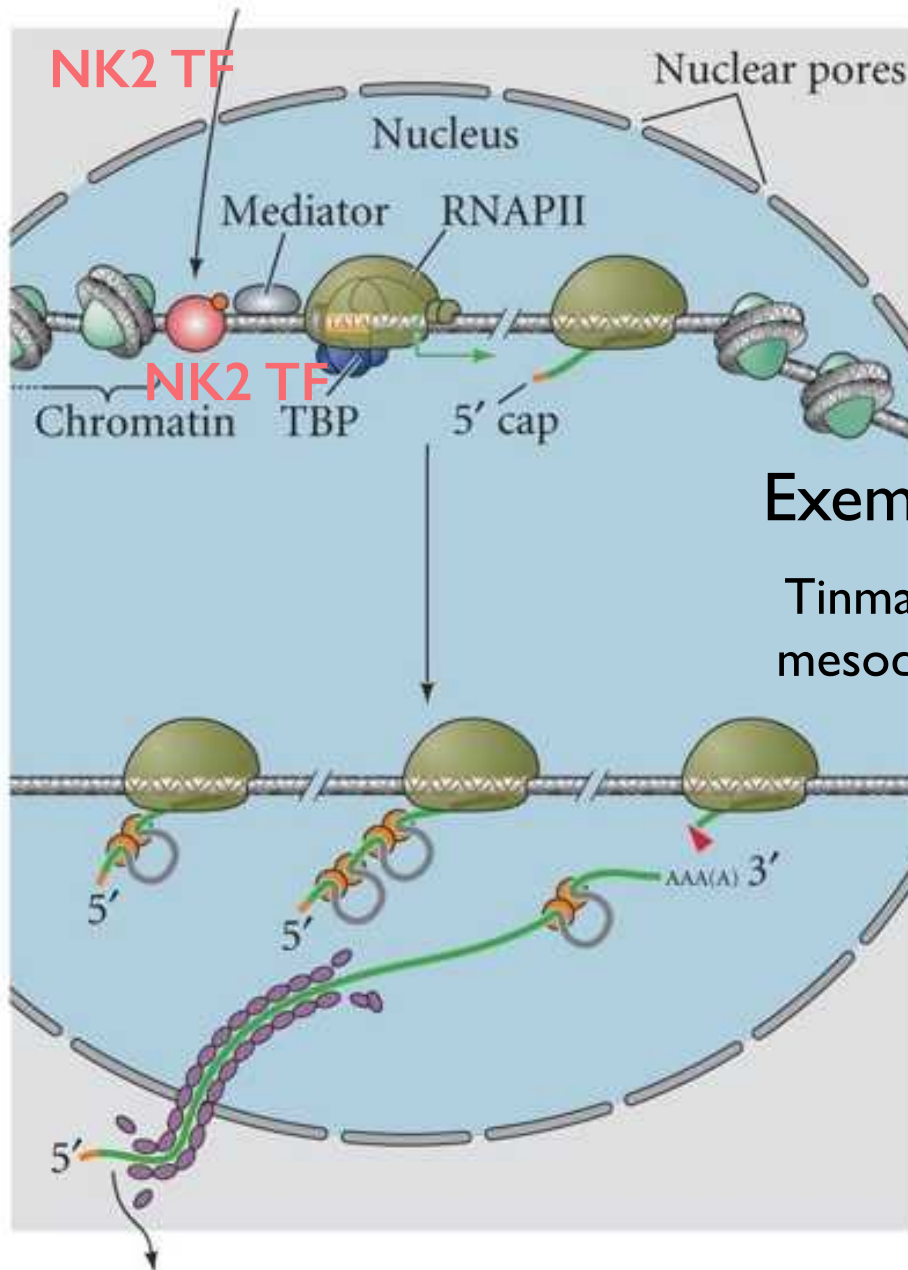
# rescate do mutante *tin*



# Genes conservados na ruta regulatória de tinman entre a mosca e o camondongo



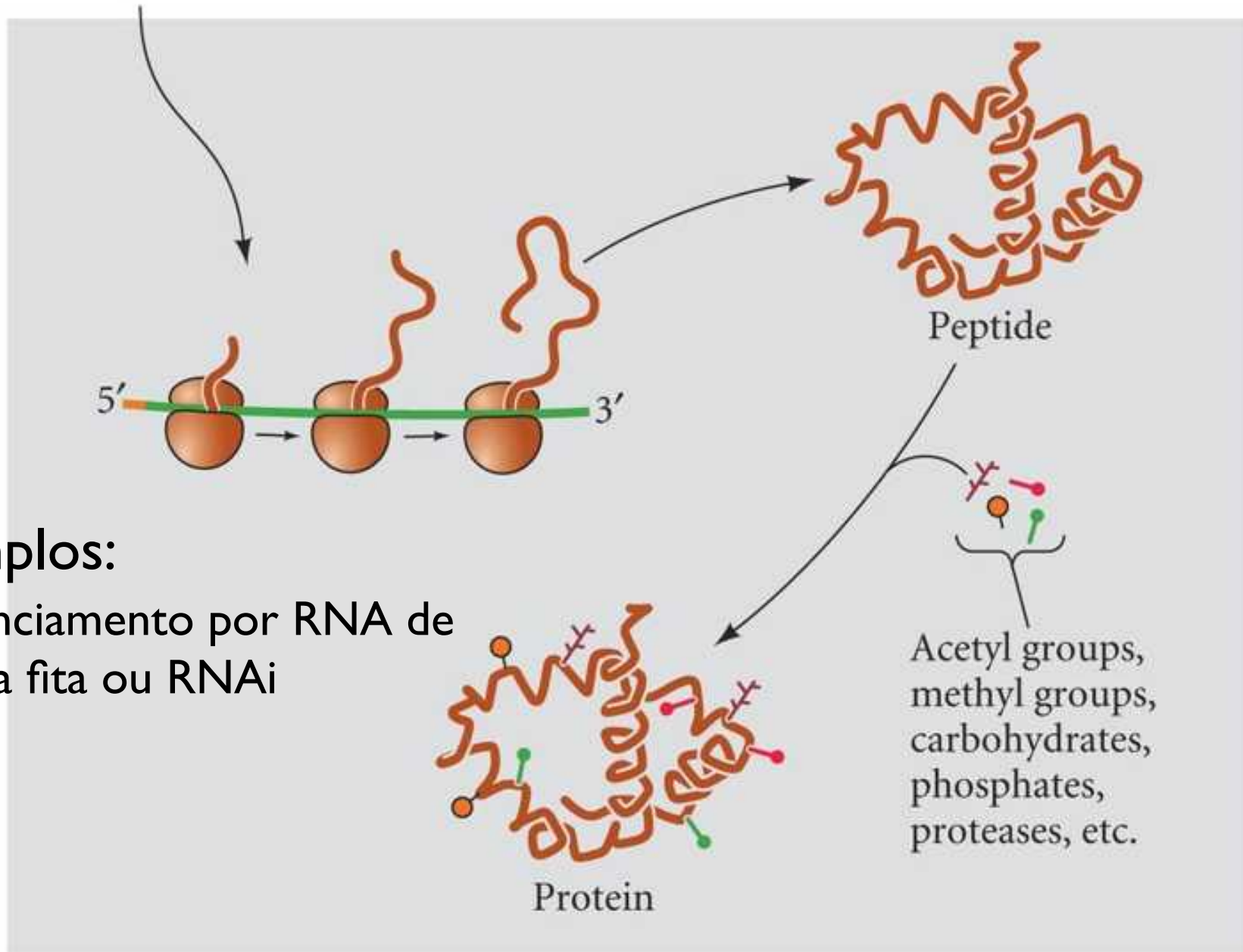
## 2) Resumo transcrição:



### Exemplo:

Tinman é necessário para a formação de mesoderme e coração.

### 3) Tradução



### Exemplos:

Silenciamento por RNA de dupla fita ou RNAi



# **TECNICA:** miRNA, siRNA, RNAi

## Estudando a função de genes por “knockdowns” genéticos

- Em nemátodos, Fire e Mello descobrem silenciamento por RNAi (1998).



# Silenciamento genético por RNA de cadeia dupla (miRNA, siRNA, RNAi)

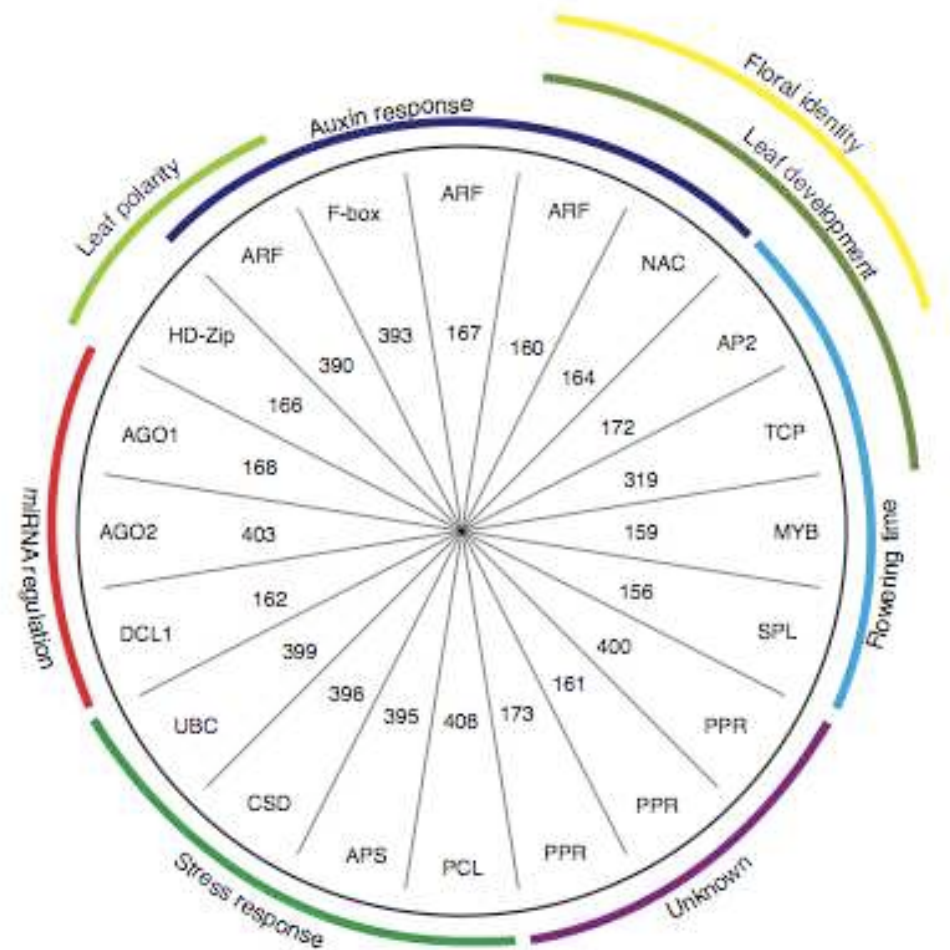
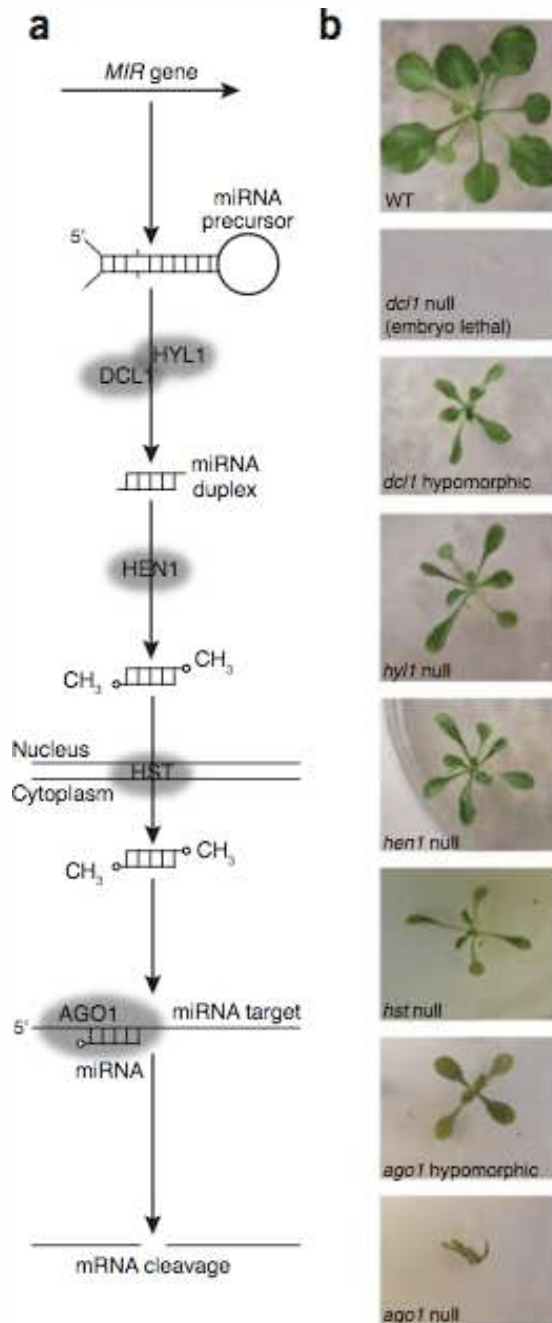


Craig Mello  
University of Massachusetts

Andrew Fire  
Stanford University

Nobel 2006

# Disrupção do silenciamento por miRNAs em plantas

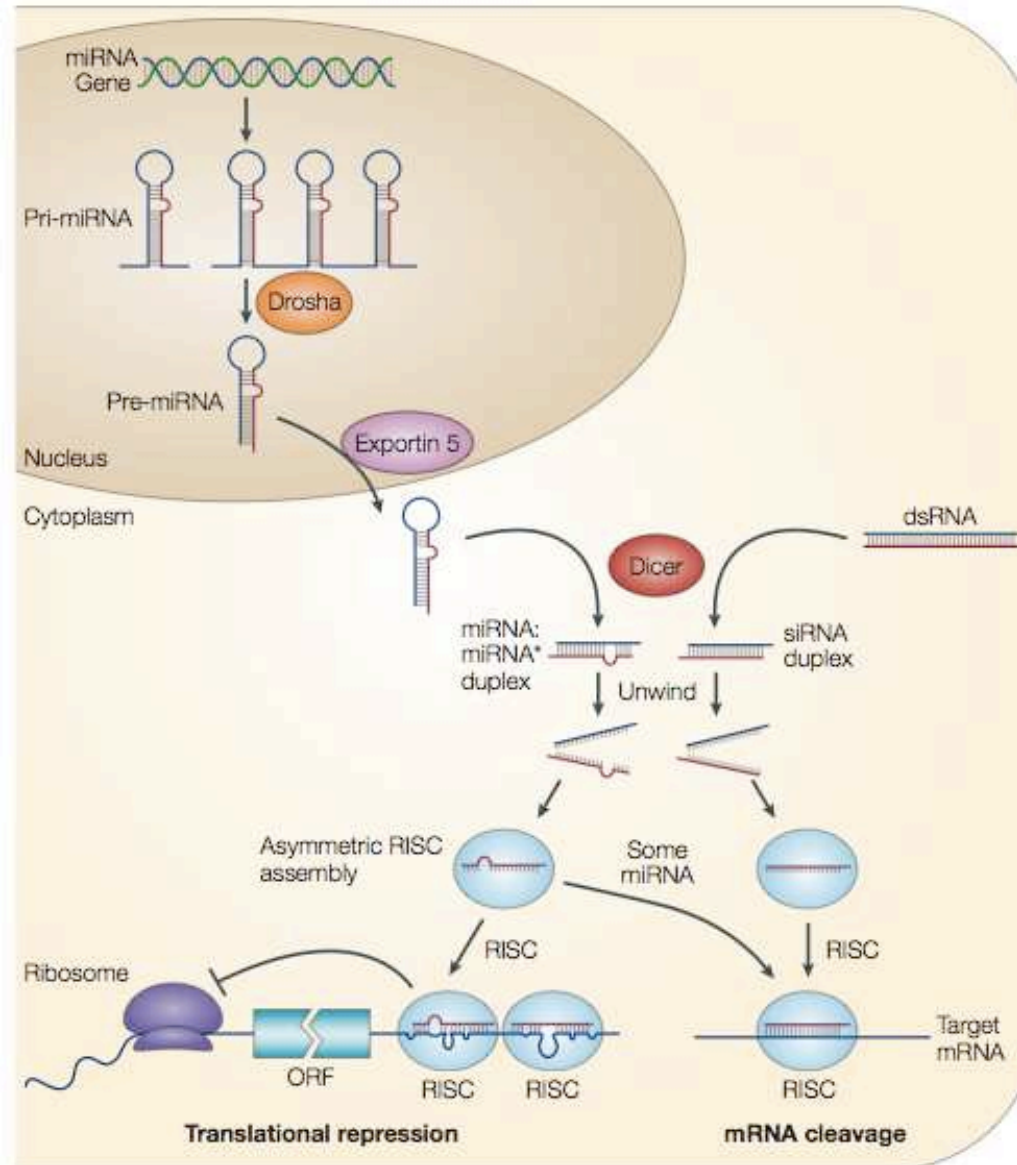


Mallory & Vaucheret, 2006



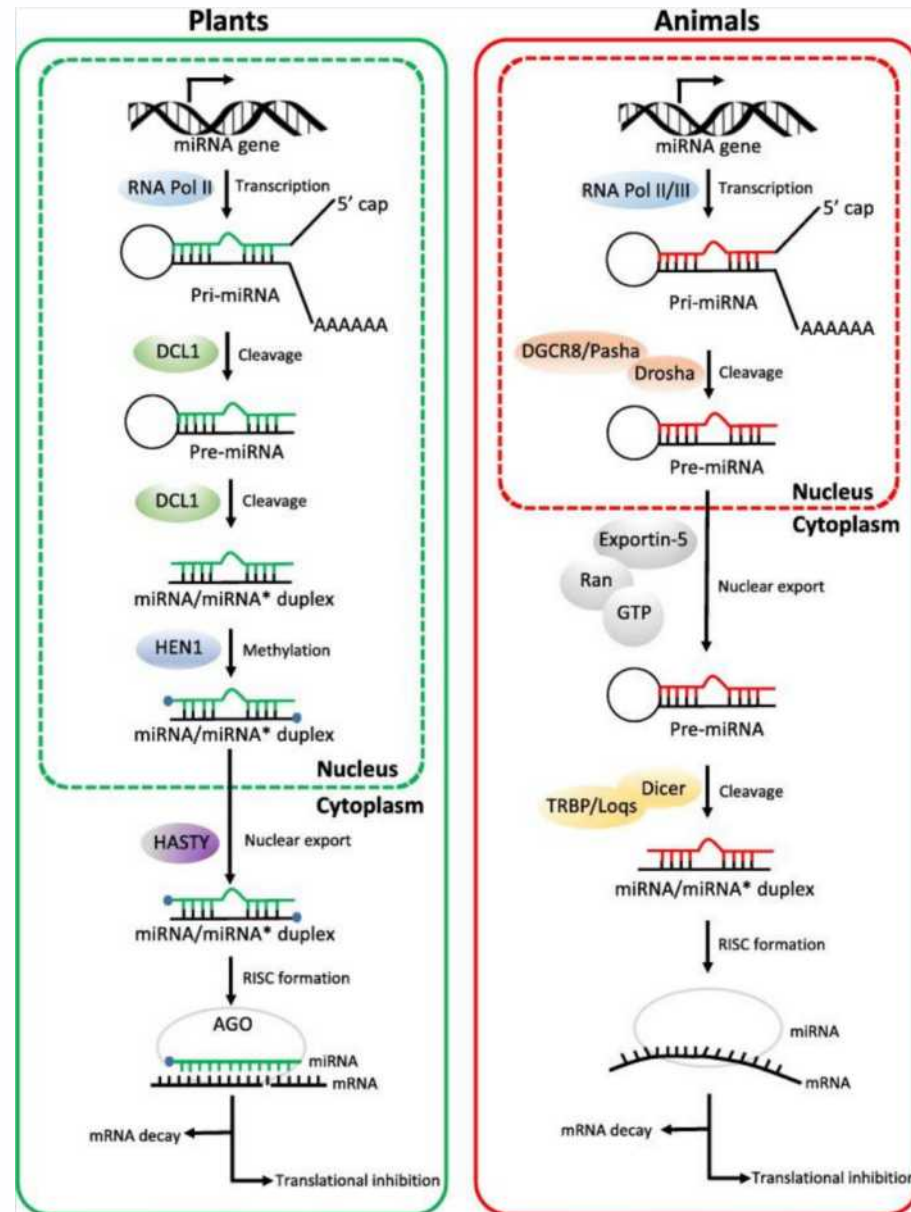
# Acção dos RNAs menores em animais

He & Hannon, 2004



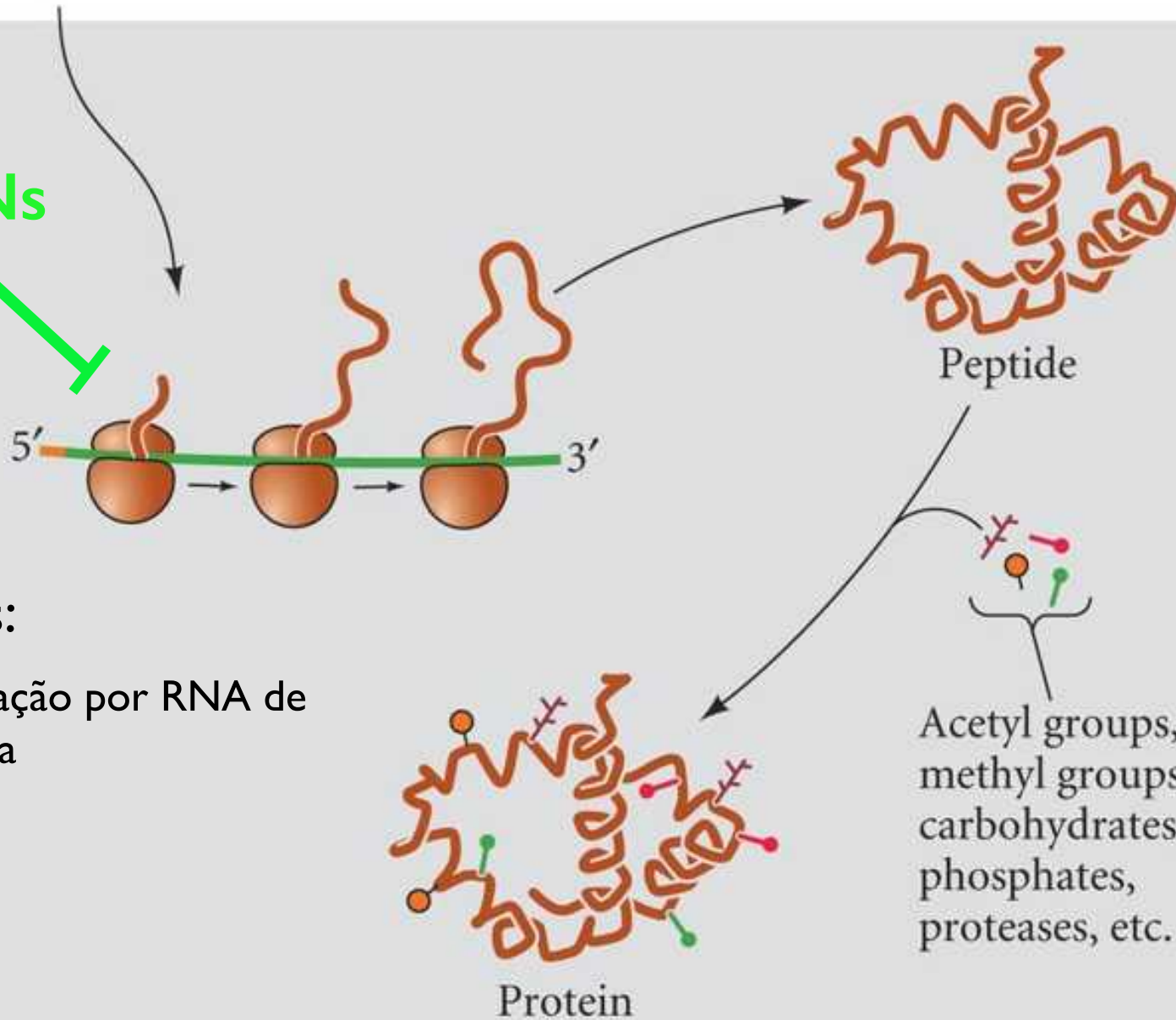


# Comparação da biogênese de miRNAs em plantas e animais



### 3) Tradução

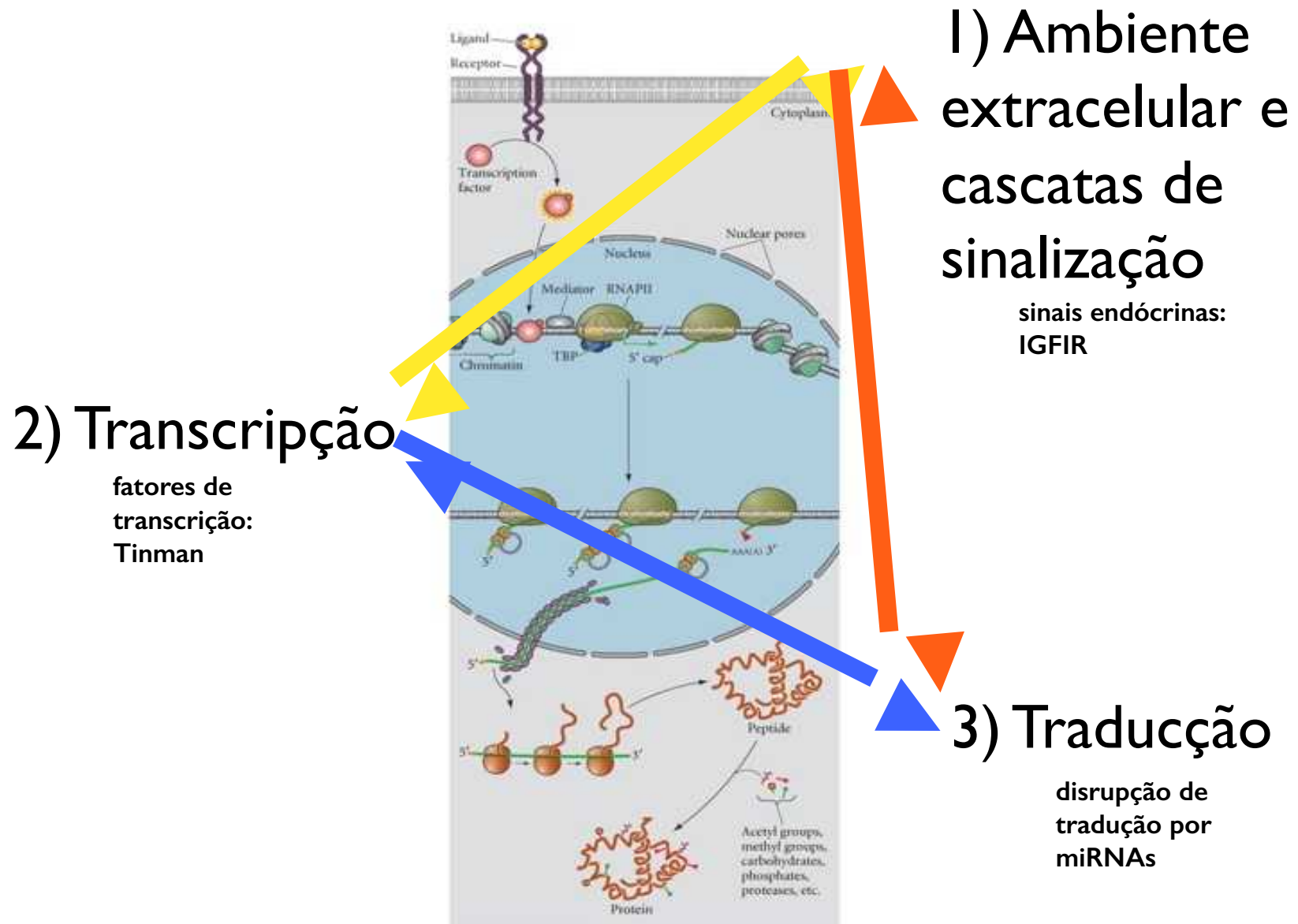
miARNs



Exemplos:

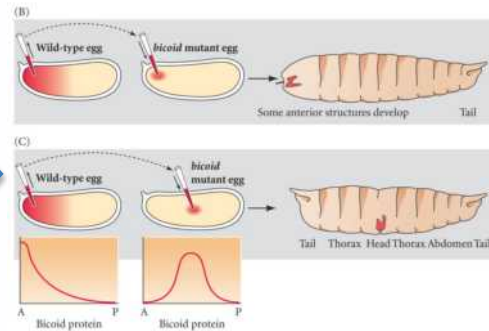
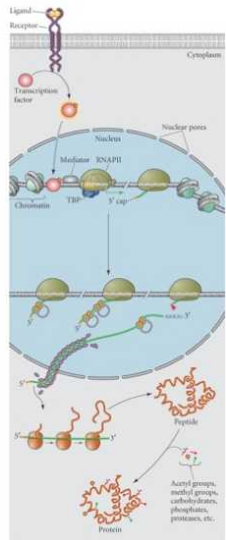
3.1) Silenciação por RNA de cadeia dupla

# A. Regulação génica: expressão dos genes pode ser regulado em vários níveis



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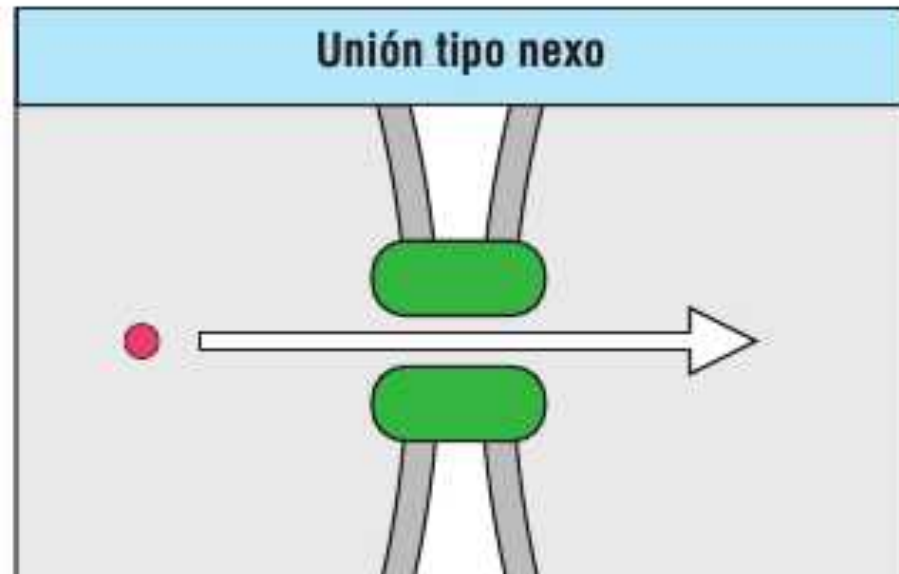
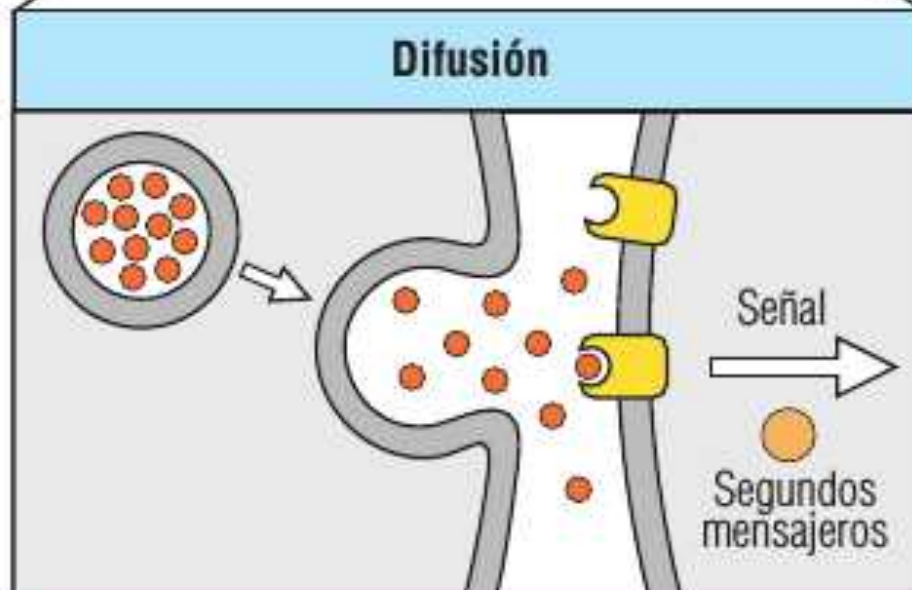
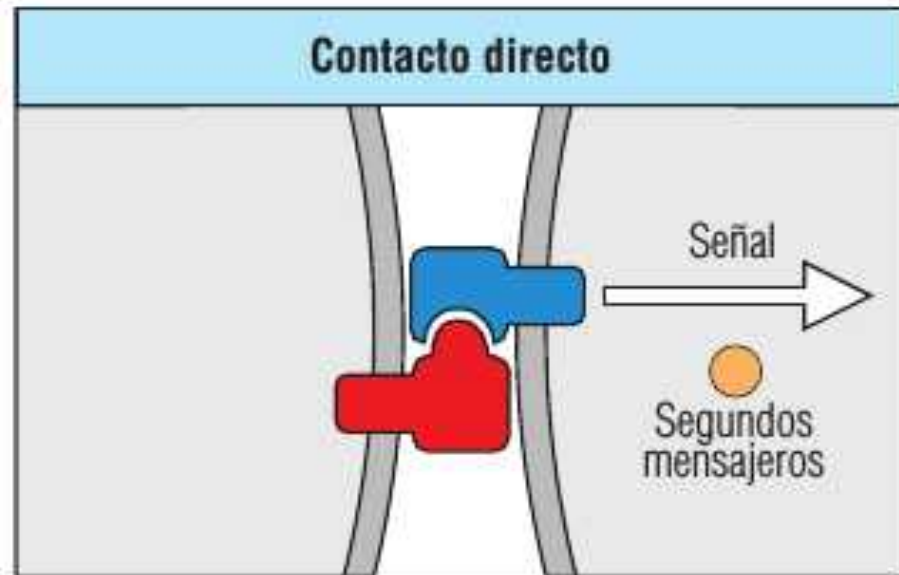
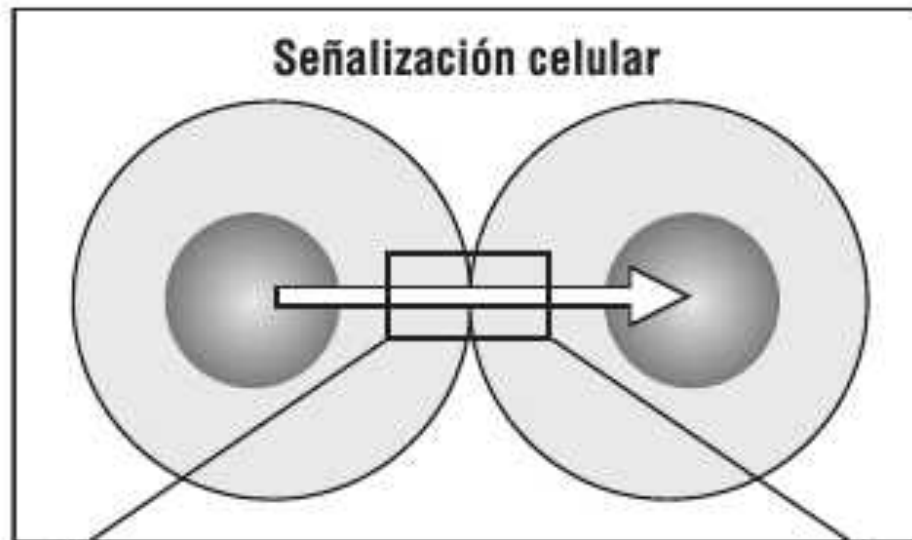
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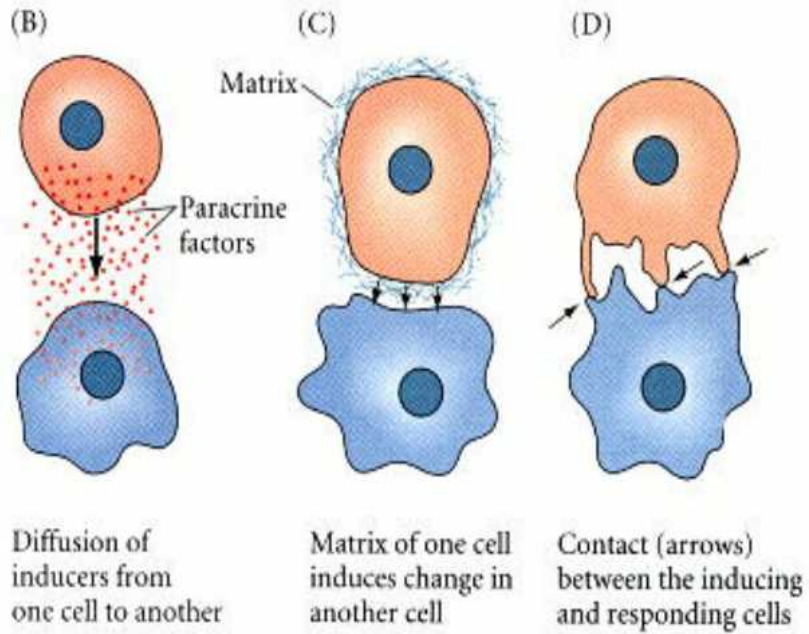
## B. Gradientes e morfógenos



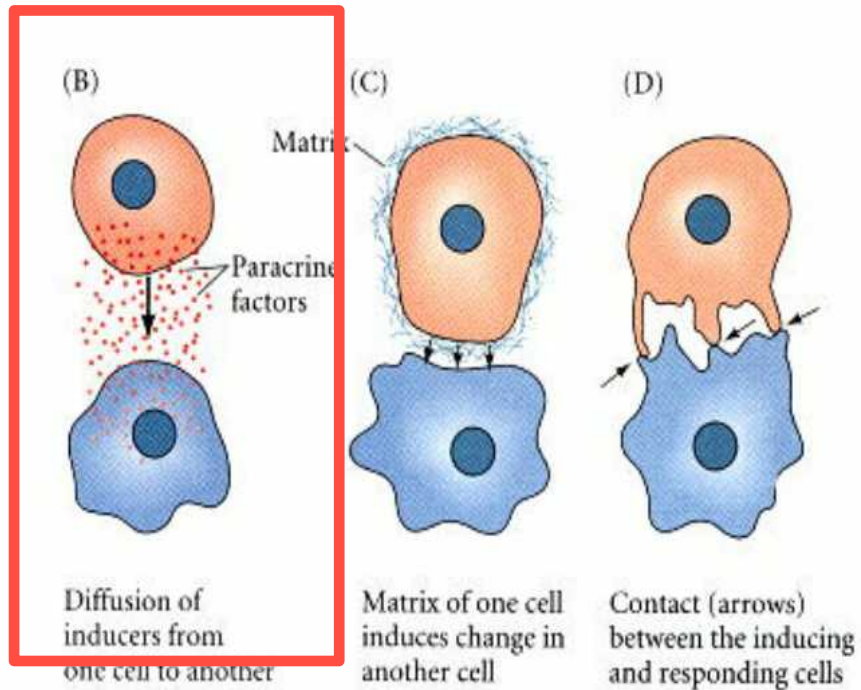
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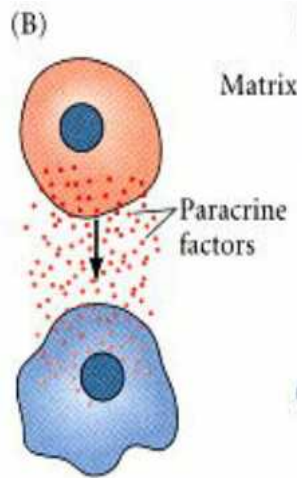


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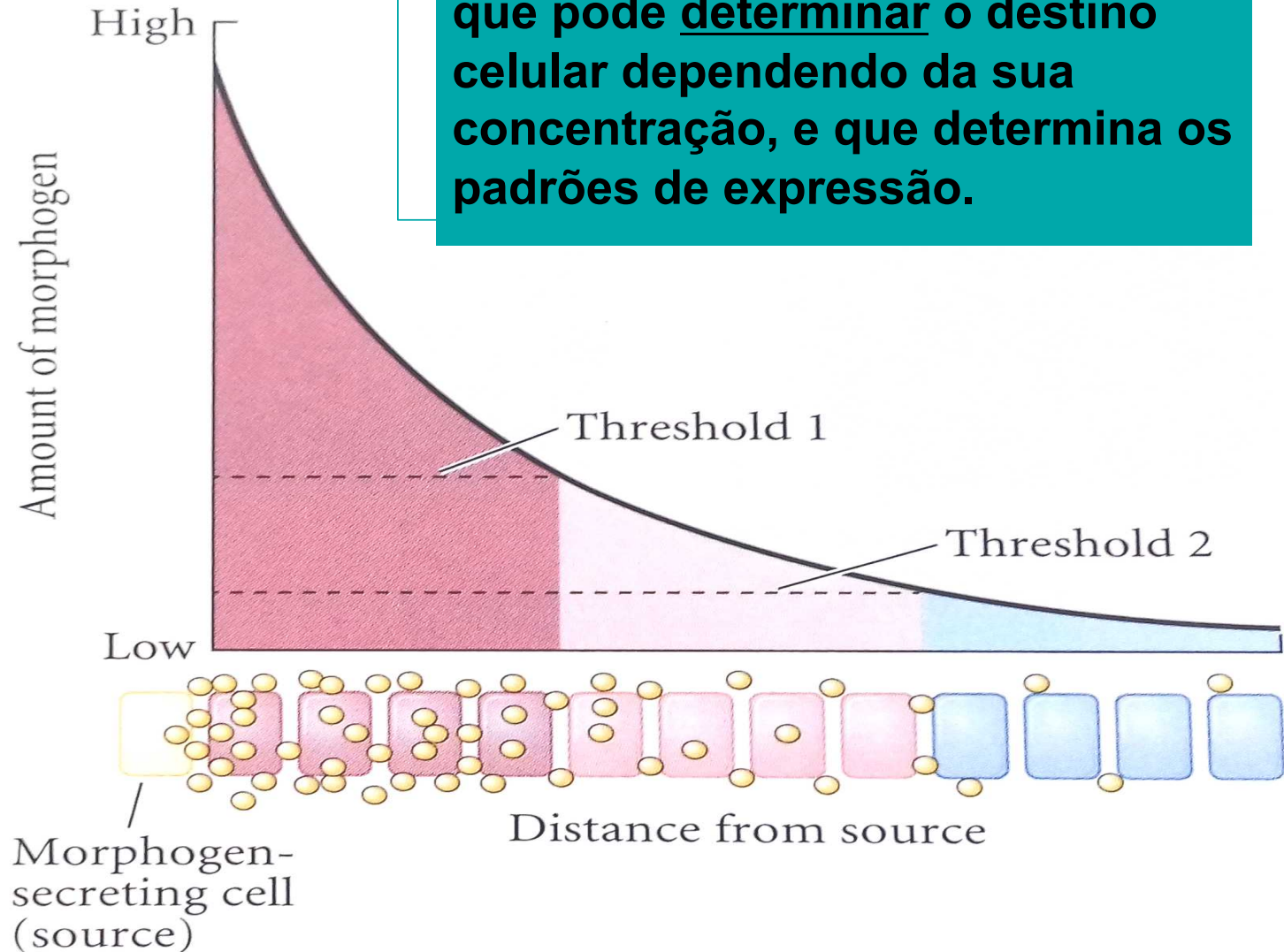


**Morfogénos: molécula difusível que pode determinar o destino celular dependendo da sua concentração, e que determina os padrões de expressão.**

# B. Gradientes e morfógenos



Diffusion of inducers from one cell to another

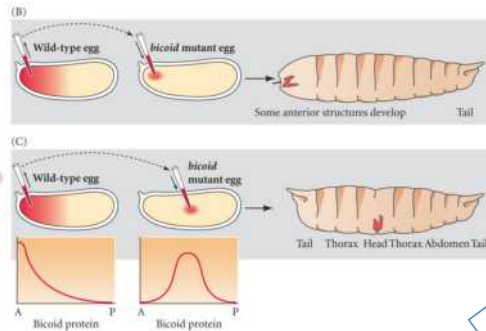
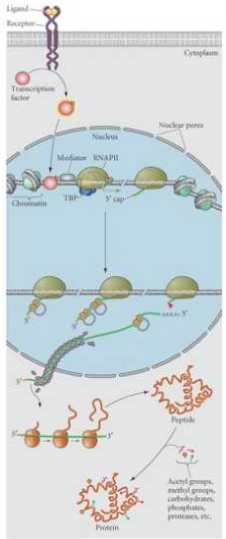


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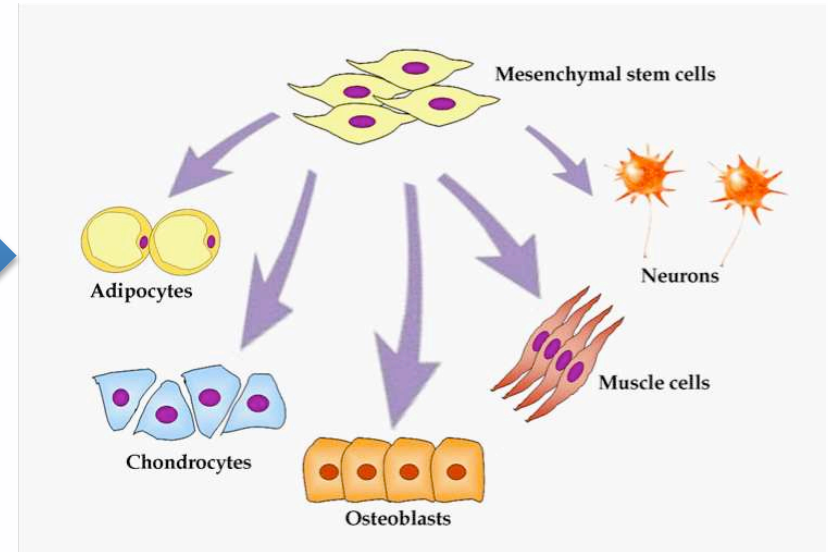
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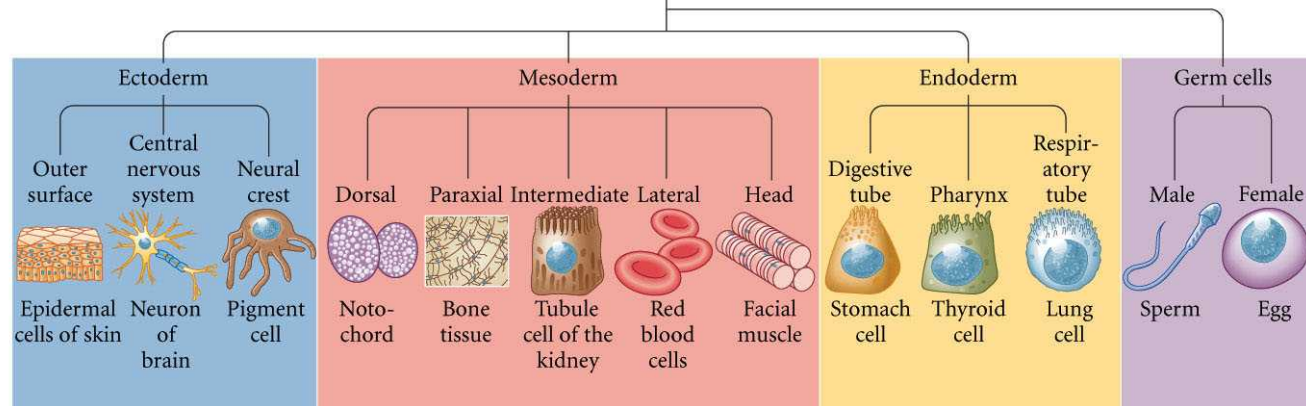
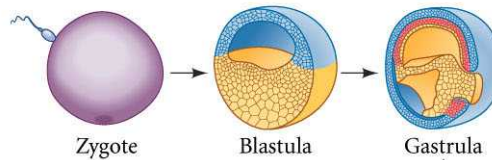
## B. Gradientes e morfógenos

## C. Especificação e diferenciação celular:



## C. Especificação e diferenciação celular embrionária:

- I. autônomo
- II. condicional
- III. (-syncycial)



# C. Especificação celular

**TABLE 3.2** Modes of cell type specification and their characteristics

## **I. Autonomous specification**

Characteristic of most invertebrates.

Specification by differential acquisition of certain cytoplasmic molecules present in the egg.

Invariant cleavages produce the same lineages in each embryo of the species. Blastomere fates are generally invariant.

Cell type specification precedes any large-scale embryonic cell migration.

Produces “mosaic” development: cells cannot change fate if a blastomere is lost.

## **II. Conditional specification**

Characteristic of all vertebrates and few invertebrates.

Specification by interactions between cells. Relative positions are important.

Variable cleavages produce no invariant fate assignments to cells.

Massive cell rearrangements and migrations precede or accompany specification.

Capacity for “regulative” development: allows cells to acquire different functions.

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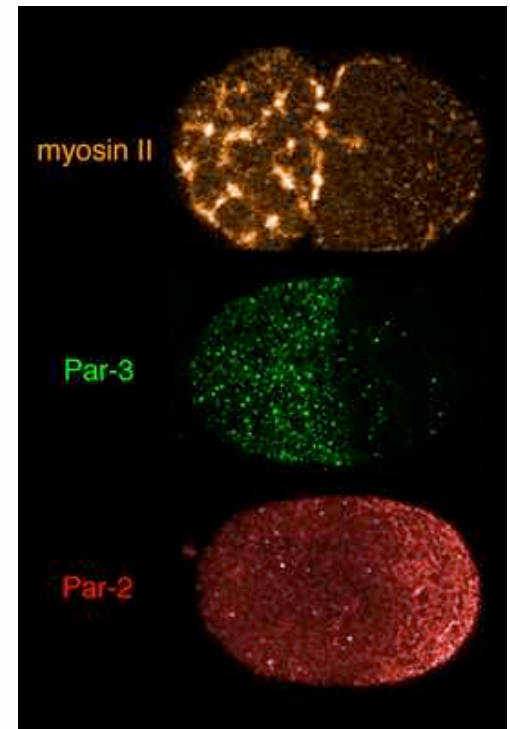
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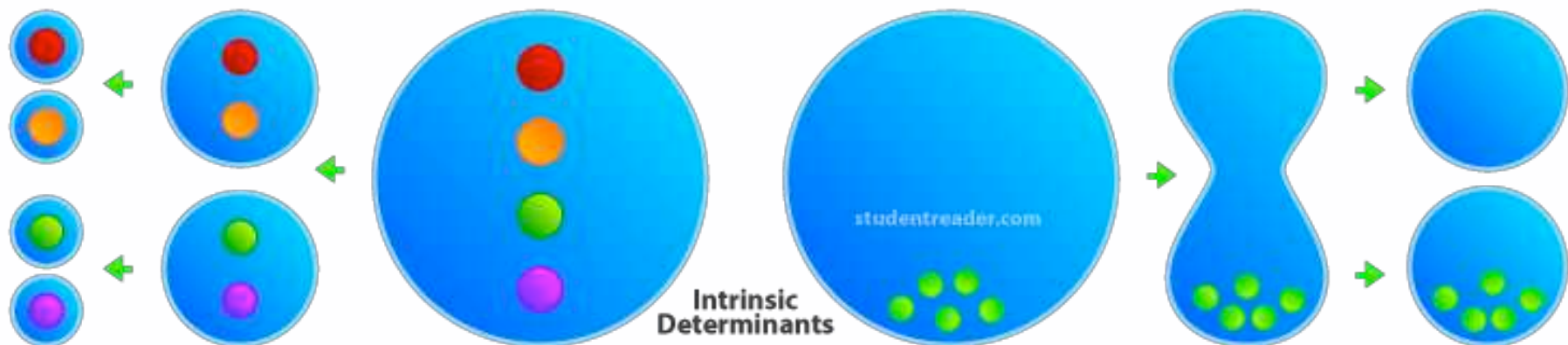
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Divisiones asimétricas: Kemphues (1988) identifica PARs en nemátodos



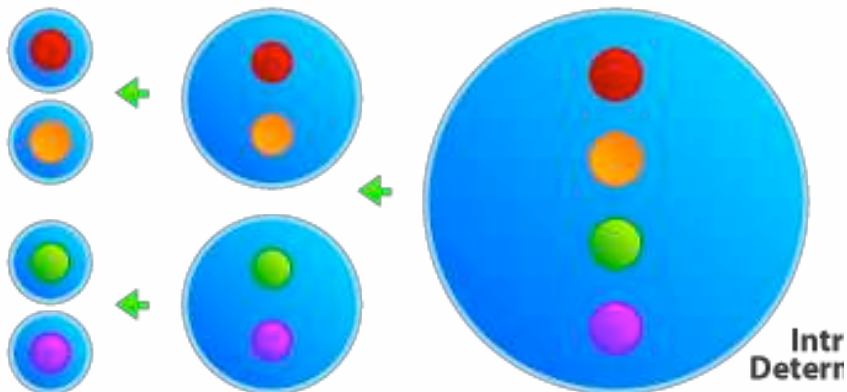
# Distribuição de determinantes durante as primeiras divisões da embriogênese resulta em **especificação autônoma**



Note: important for preformation, autonomous development, determinative development



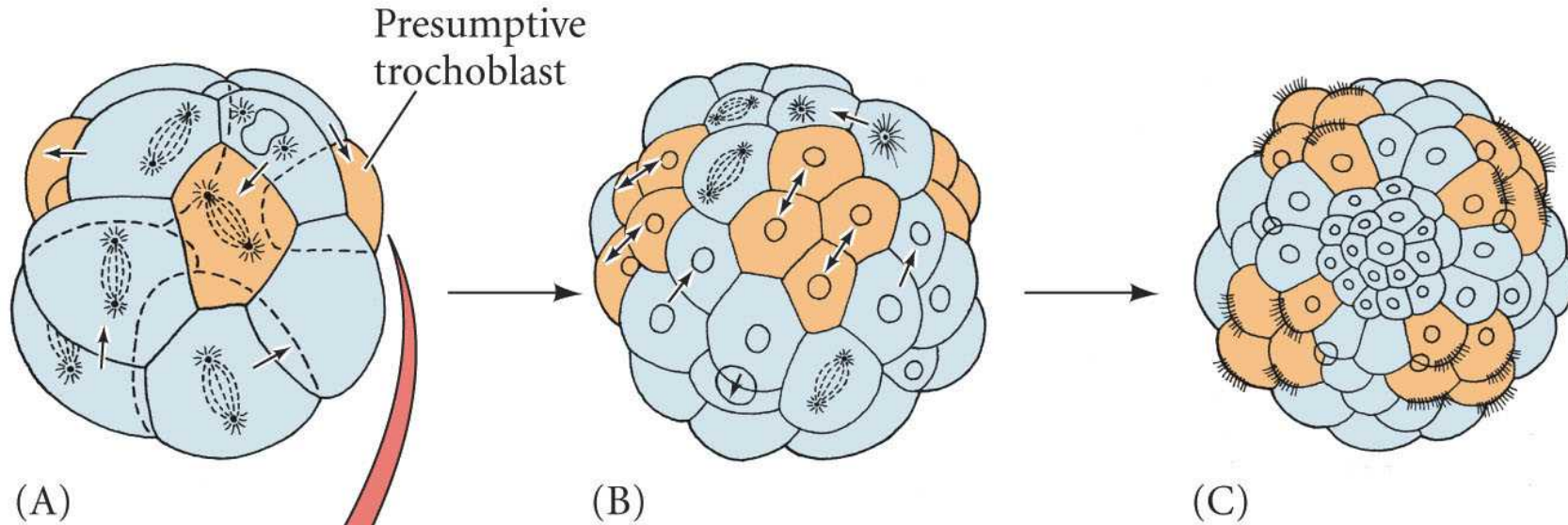
# Distribuição de determinantes intrínsecos durante as primeiras divisões da embryogênese resulta em **especificação autônoma**



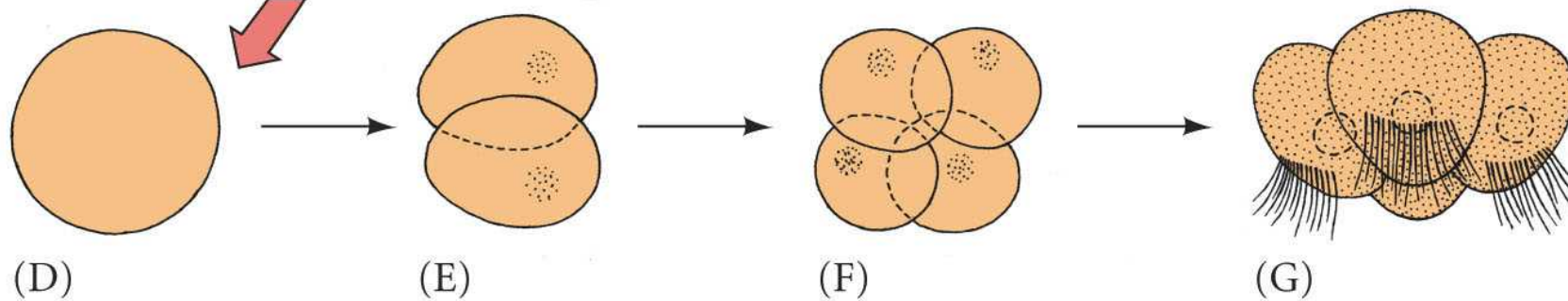
Note: important for preformation, autonomous development, determinative development

# Especificação autónoma nos espiralados (lapas-gastrópodos-Mollusca)

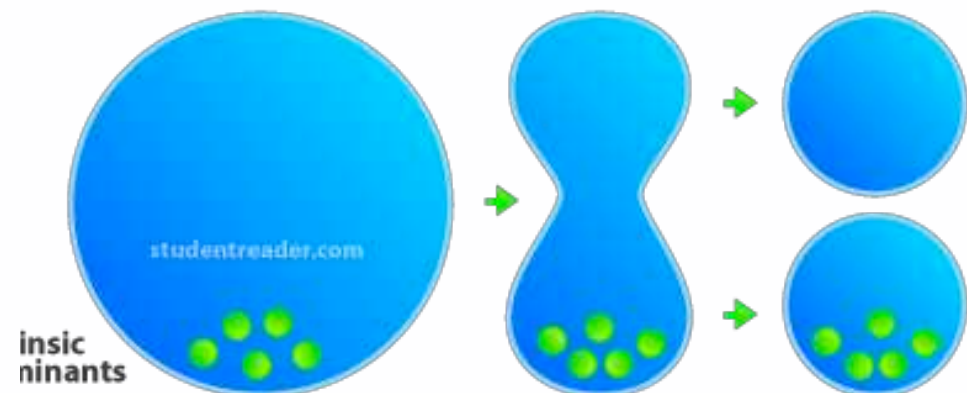
Normal development of *Patella*



Isolated trochoblast development

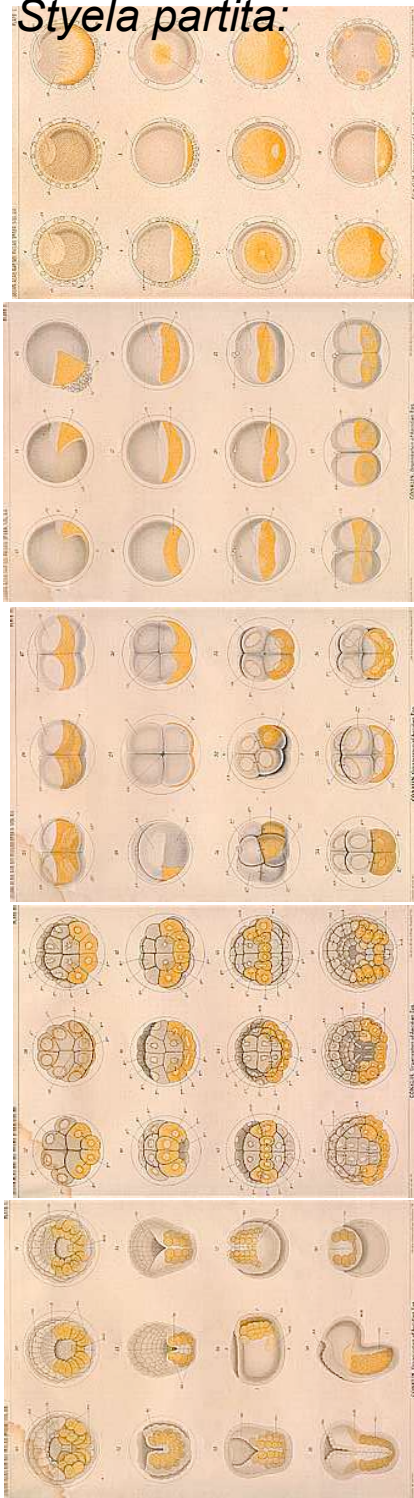


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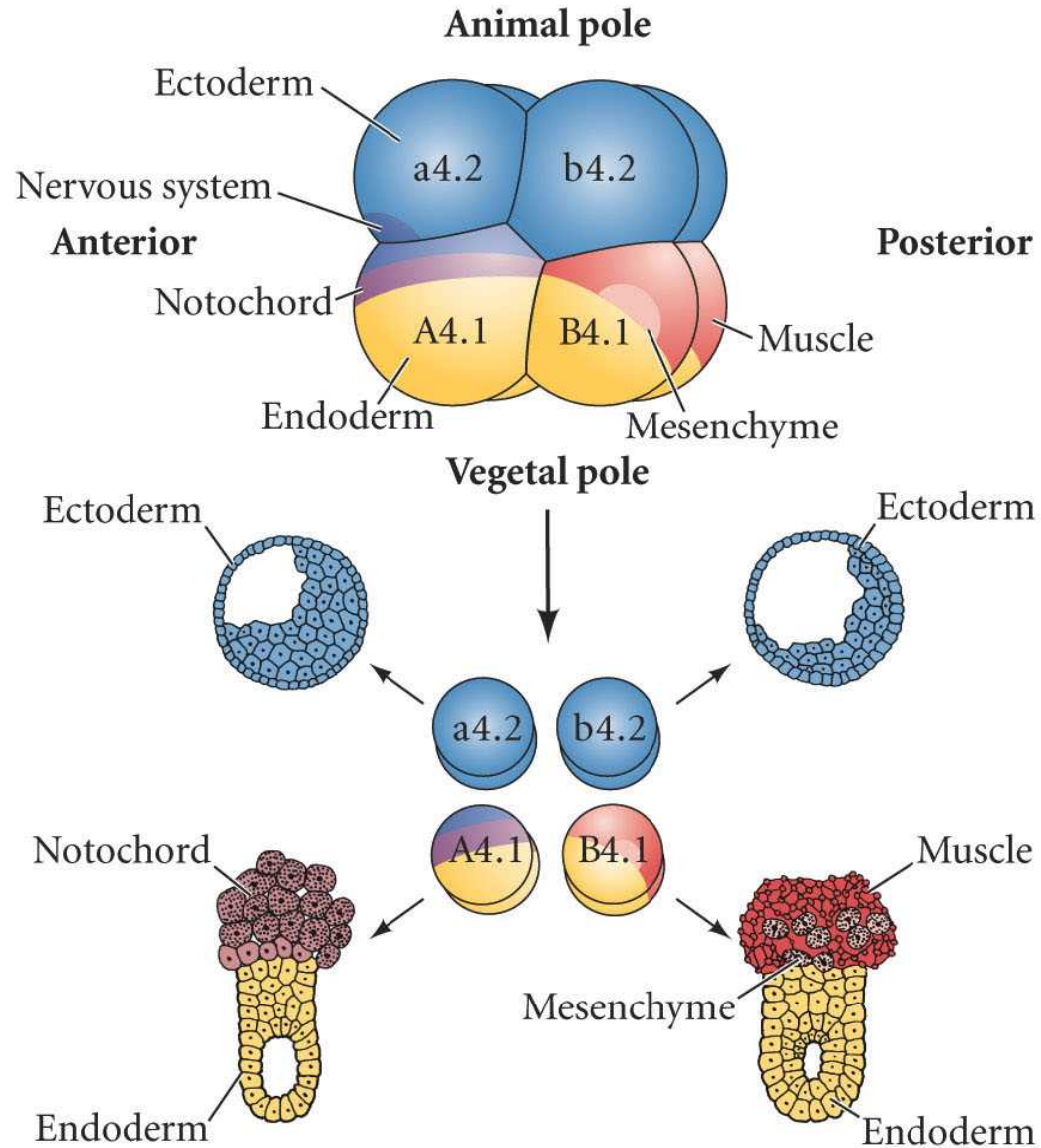


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*Styela partita*:

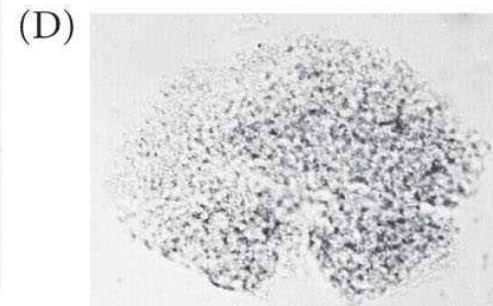
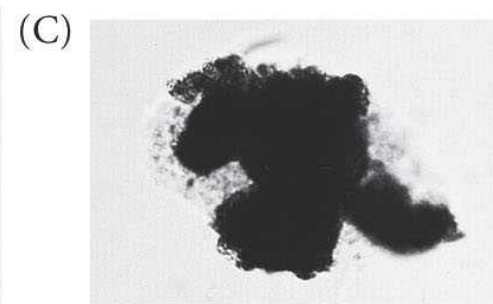
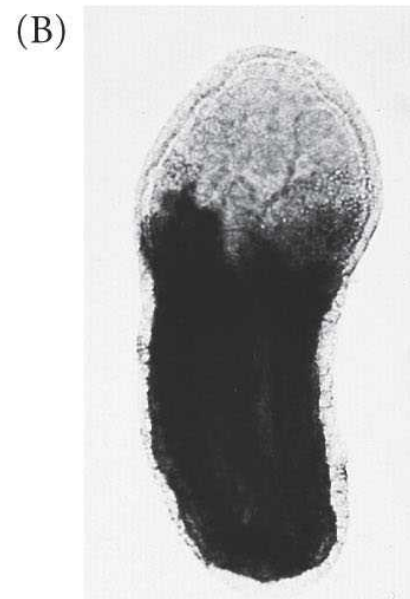
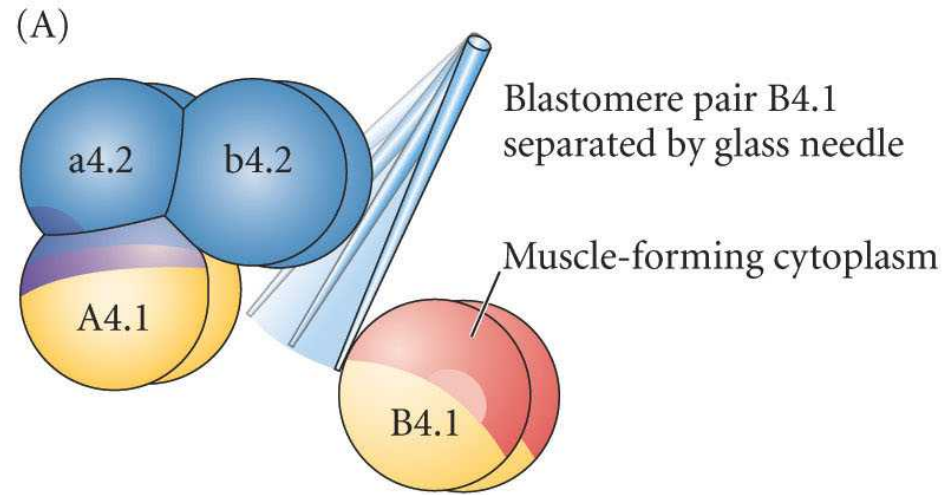
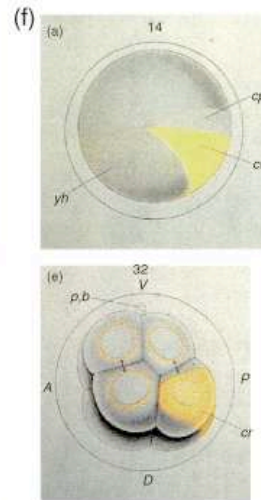


# Especificação autônoma em ascídias

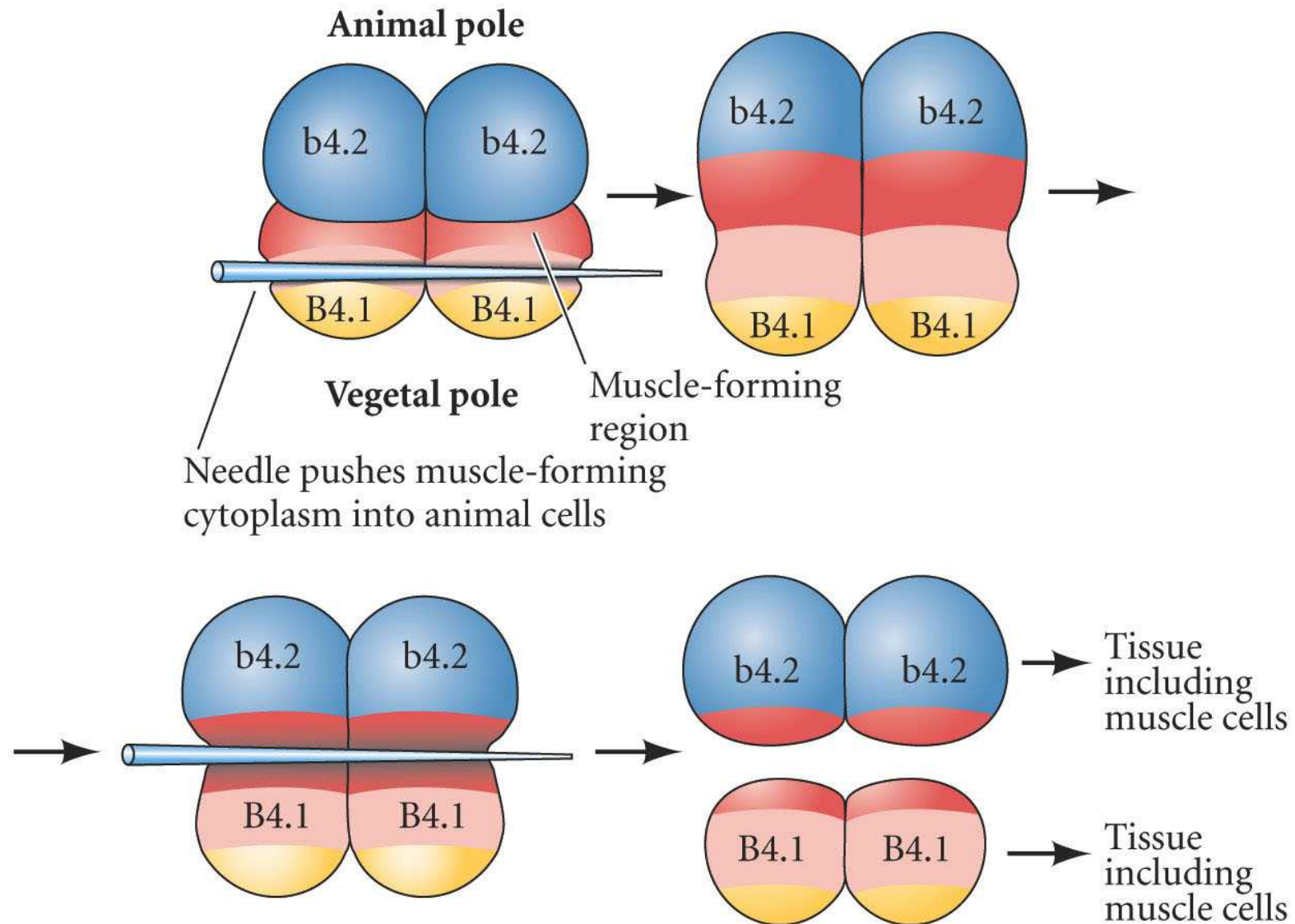




# Desenvolvimento do músculo em tunicados (Cordata)



# Citoplasma amarelo contem determinantes de células musculares da larva



# C. Especificação celular

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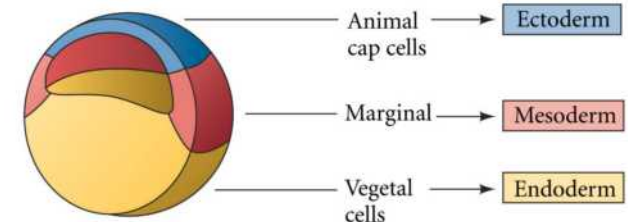
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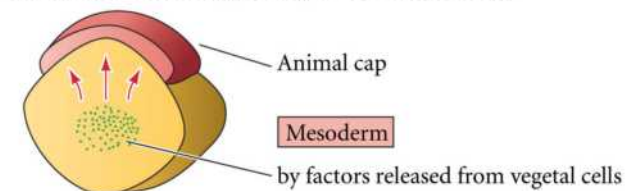
Massive cell rearrangements and migrations precede or accompany specification.

Capacity for “regulative” development: allows cells to acquire different functions.

(A) Dissected blastula fragments give rise to different tissue in culture:

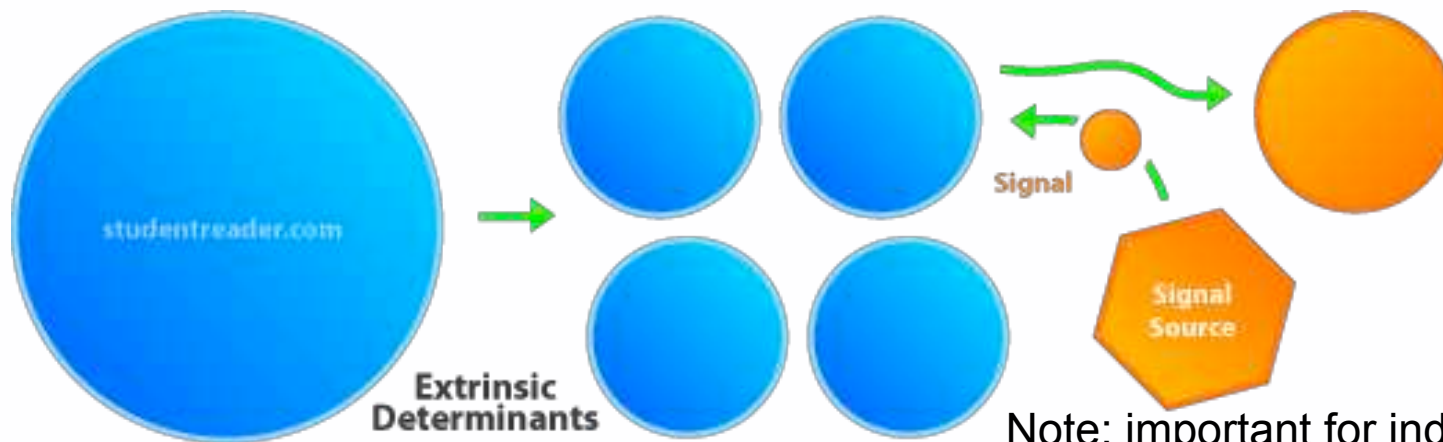


(B) Animal and vegetal fragments give rise to mesoderm



Mesoderm induction (1969): Nieuwkoop, JMW Slack, Kimmelman & Kirschner, and JC Smith find that FGF and TGF- $\beta$  is important

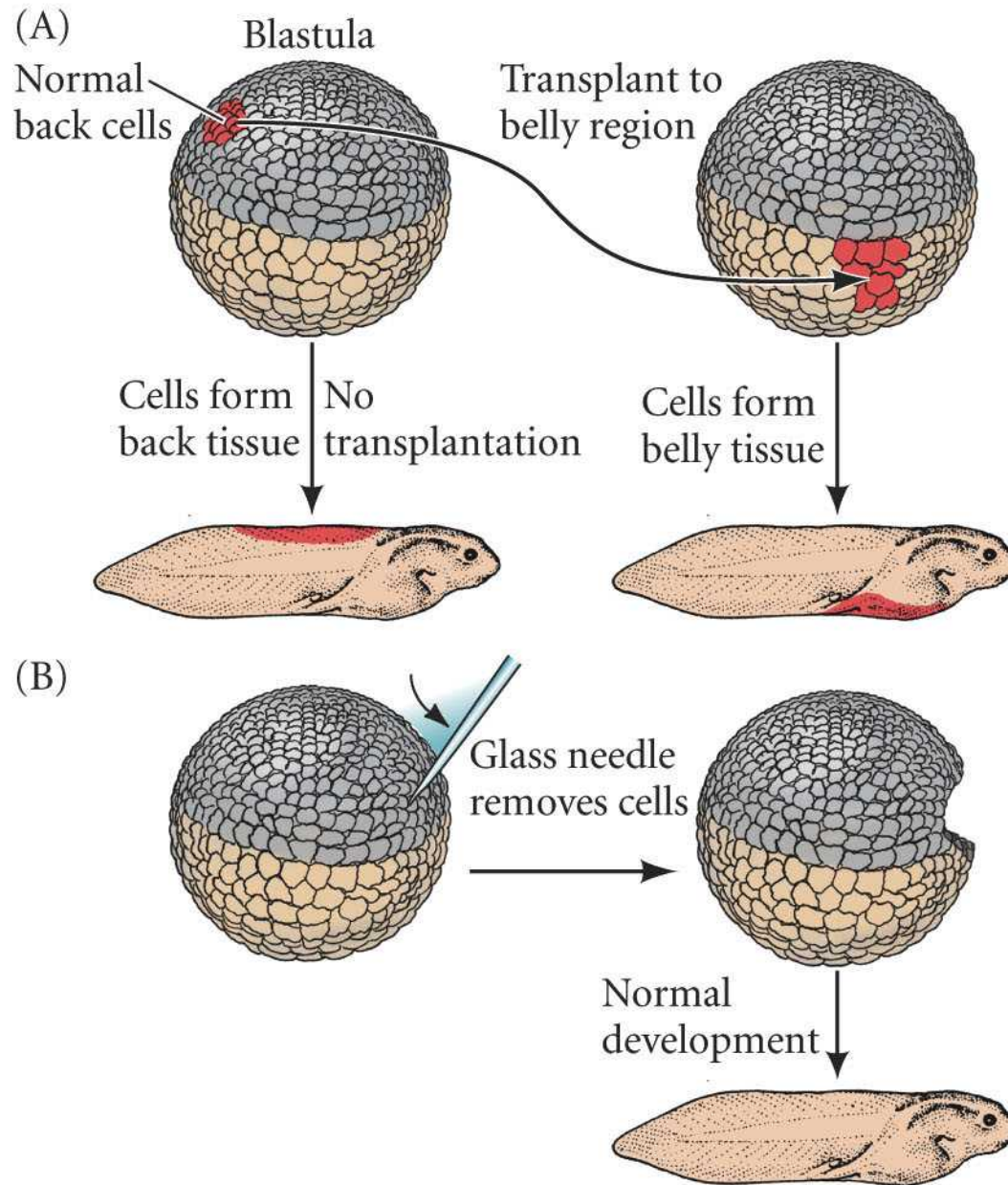
# Distribuição de determinantes extrínsecos durante a embriogênese resulta em **especificação condicional**



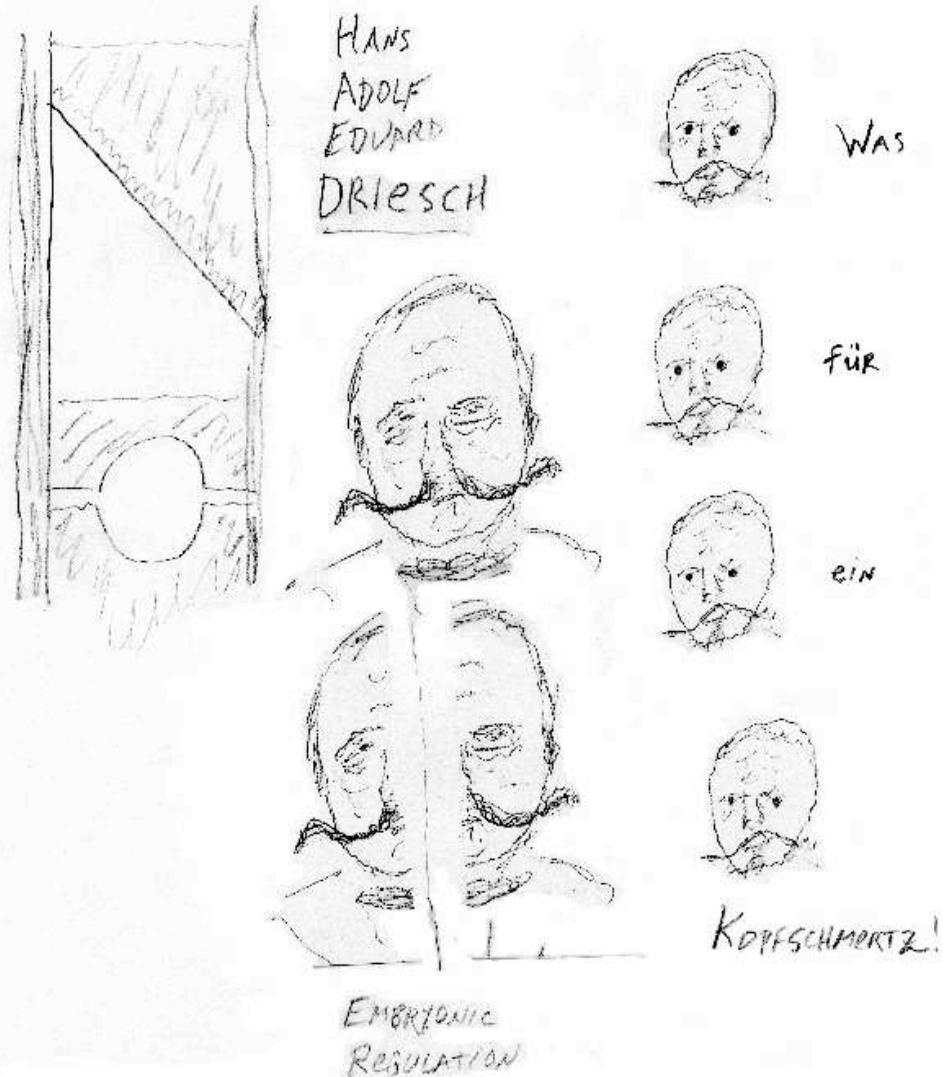
Note: important for induction, regulative development, conditional specification



# Especificação condicional



# Especificação condicional



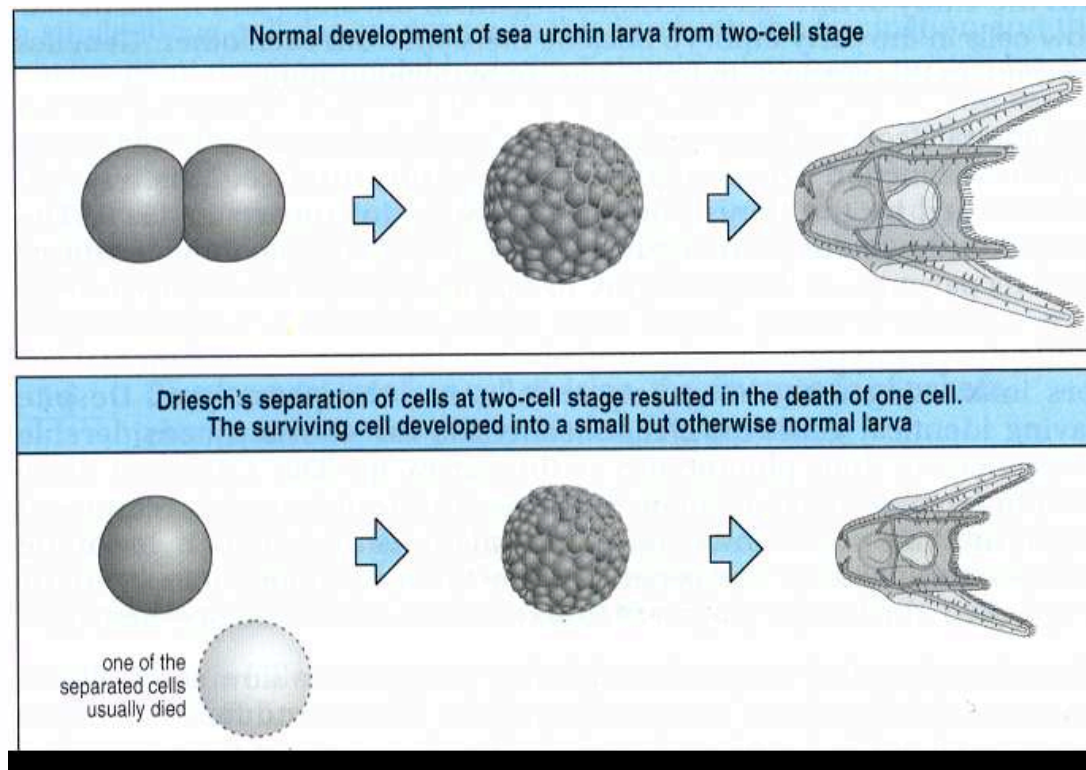
# Especificação condicional



A verdadeira ameaça  
e dor de cabeça...



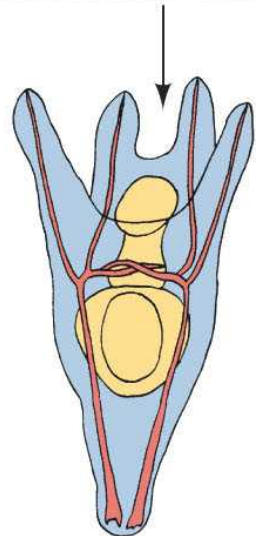
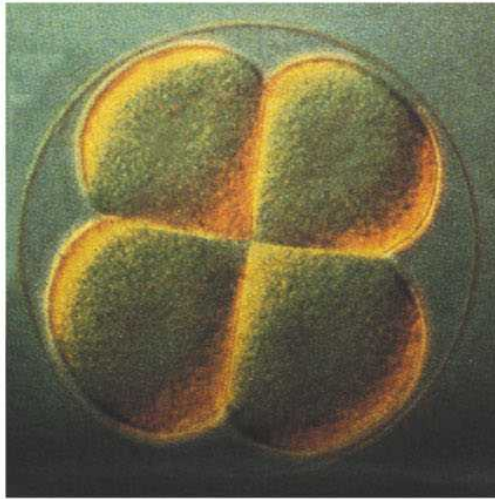
# Especificação condicional: desenvolvimento regulativo em ouriços



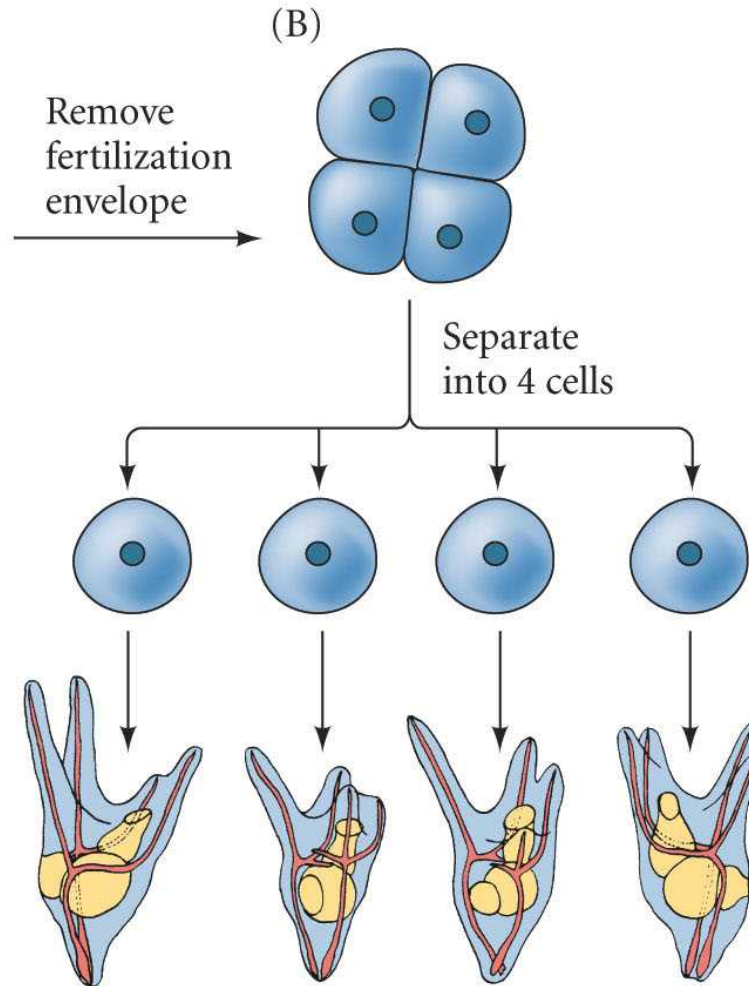


# Especificação condicional: desenvolvimento regulativo em ouriços

(A) Fertilization envelope



Normal pluteus larva



Plutei developed from single cells of 4-cell embryo

*“Development starts with a few ordered manifoldnesses; but the manifoldnesses create, by interactions, new manifoldnesses, and these are able, by acting back on the original ones, to provoke new differences, and so on. With each new response, a new cause is immediately provided, and a new specific reactivity for further specific responses. We derive a complex structure from a simple one given in the egg.”*



# C. Especificação celular

**TABLE 3.2** Modes of cell type specification and their characteristics

## I. Autonomous specification

Characteristic of most invertebrates.

Specification by differential acquisition of certain cytoplasmic molecules present in the egg.

Invariant cleavages produce the same lineages in each embryo of the species. Blastomere fates are generally invariant.

Cell type specification precedes any large-scale embryonic cell migration.

Produces “mosaic” development: cells cannot change fate if a blastomere is lost.

## II. Conditional specification

Characteristic of all vertebrates and few invertebrates.

Specification by interactions between cells. Relative positions are important.

Variable cleavages produce no invariant fate assignments to cells.

Massive cell rearrangements and migrations precede or accompany specification.

Capacity for “regulative” development: allows cells to acquire different functions.

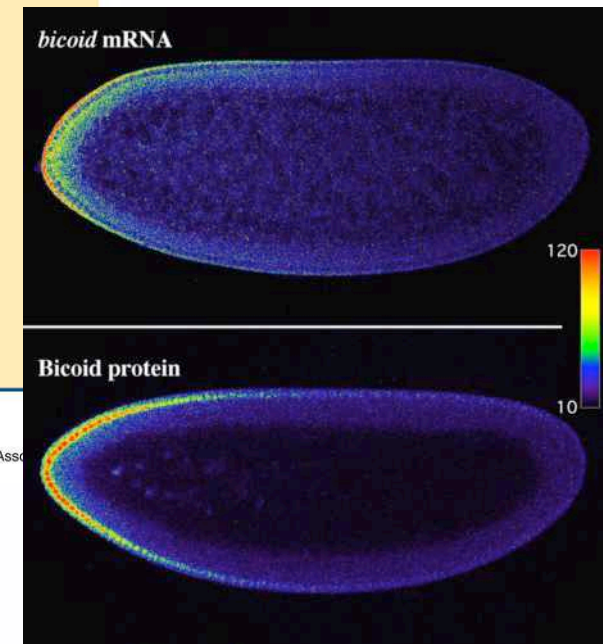
## III. Syncytial specification

Characteristic of most insect classes.

Specification of body regions by interactions between cytoplasmic regions prior to cellularization of the blastoderm.

Variable cleavage produces no rigid cell fates for particular nuclei.

After cellularization, conditional specification is most often seen.

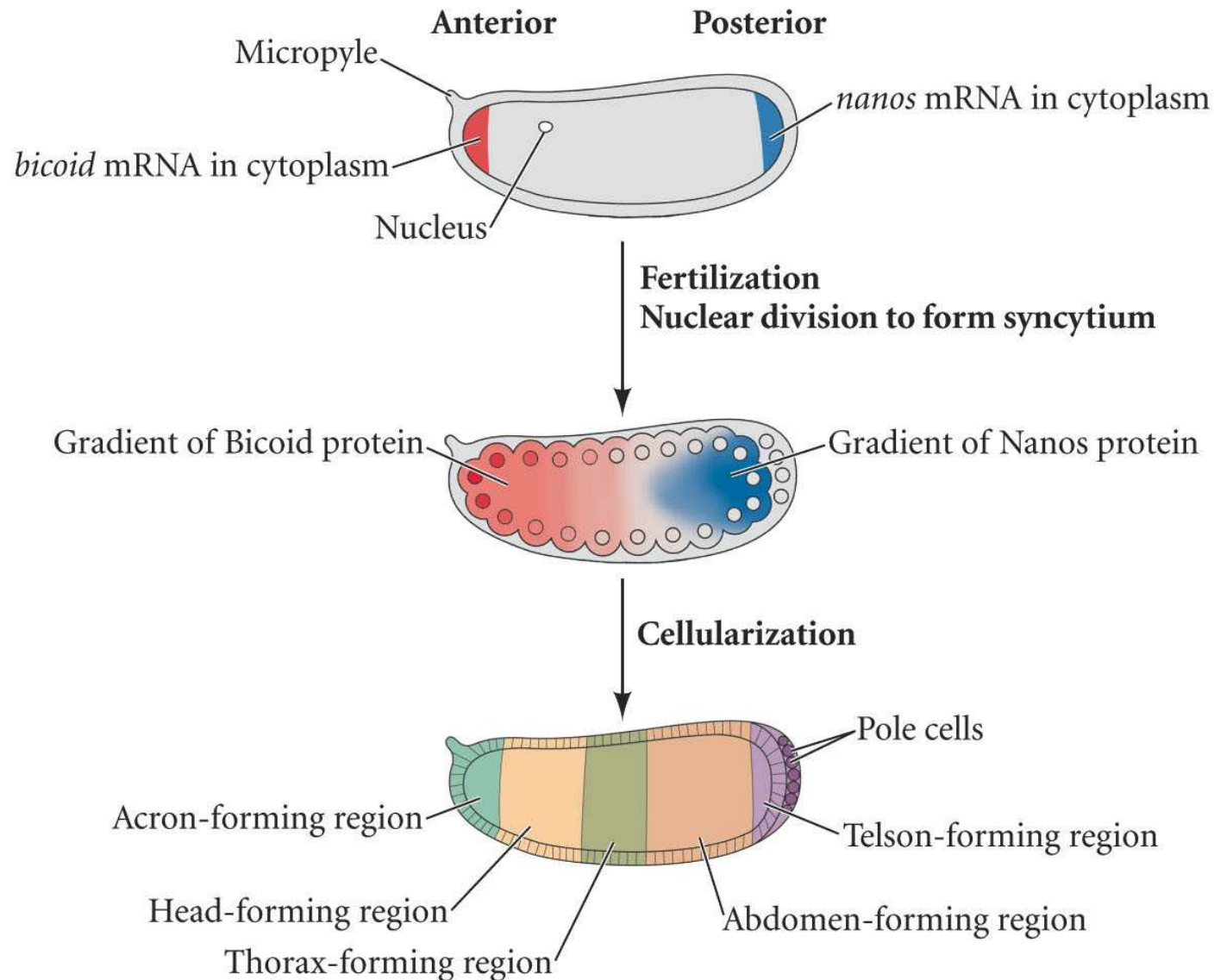


Source: After Davidson 1991.

DEVELOPMENTAL BIOLOGY, Eighth Edition, Table 3.2 © 2006 Sinauer Ass

Gradientes de morfógenos: Fronhofer, Dravis y Nusslein  
Volhardt (1986) identifican Bicoid como morfógeno

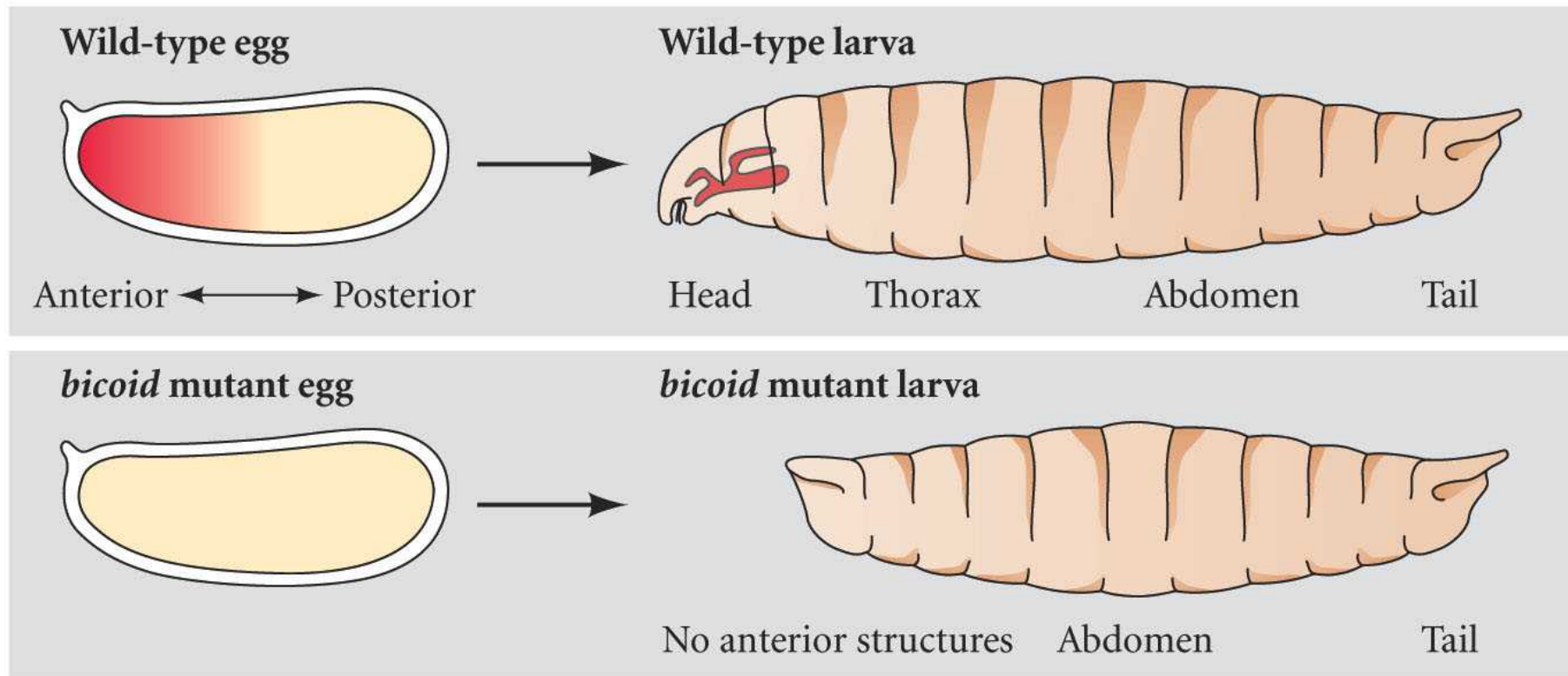
**Especificação sincicial:** Distribuição de determinantes intrínsecos antes da celularização (formação das primeiras células) resulta na especificação de regiões corpóreas (autónoma), e determinantes extrínsecos regulam a especificação após a celularização (condicional)





# Proteína Bicoid es el morfógeno de cabeza en *Drosophila*

(A)

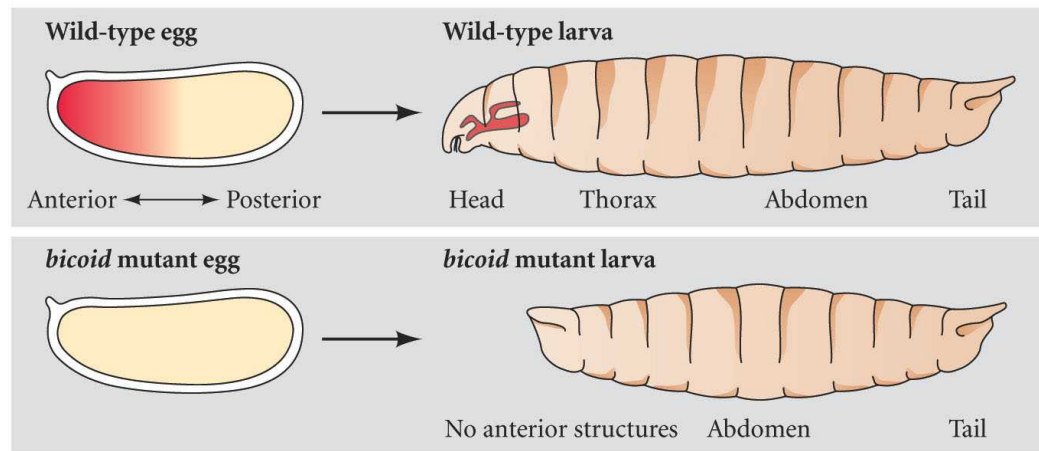




# Proteína Bicoid é o morfógeno ou determinante de cabeça em *Drosophila*

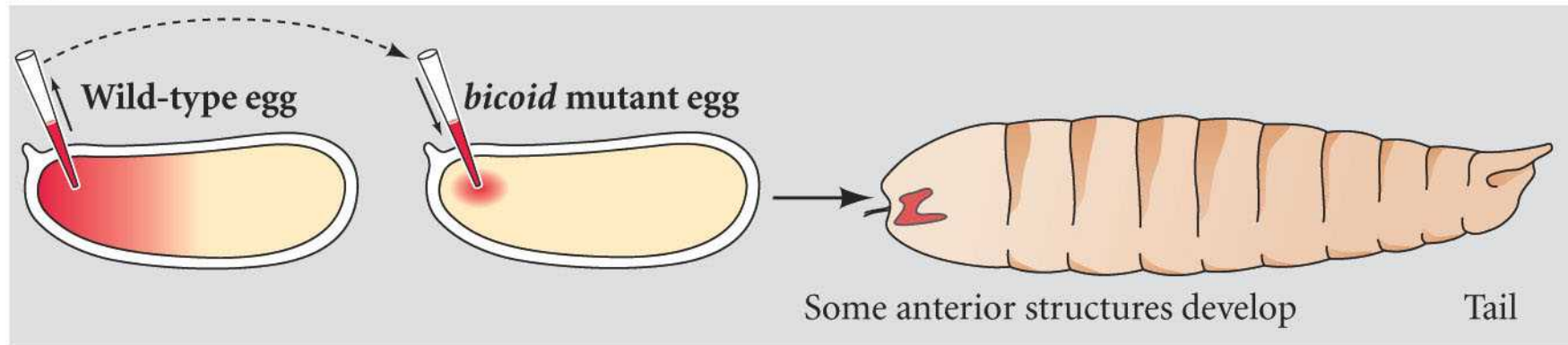
Discuta: Experimentos adicionais para comprovar que o Bicoid é o morfógeno determinante da cabeça?

(A)

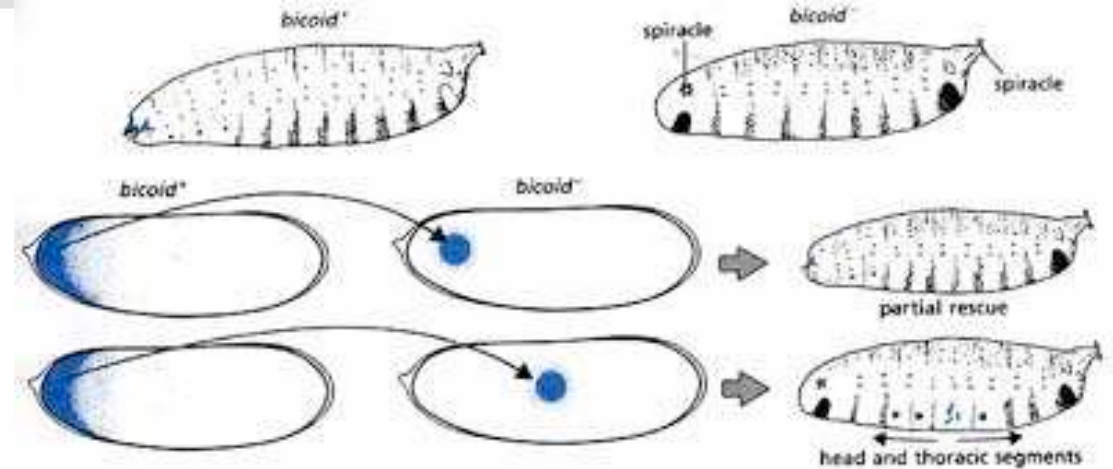
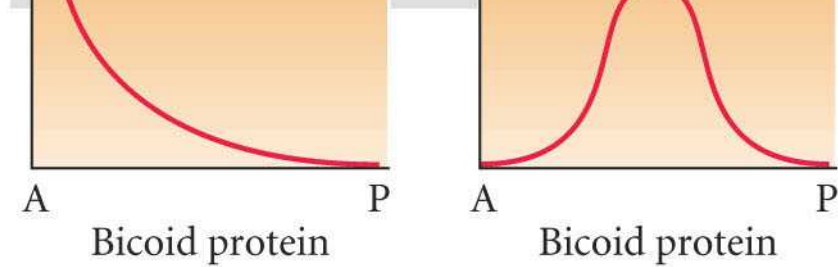
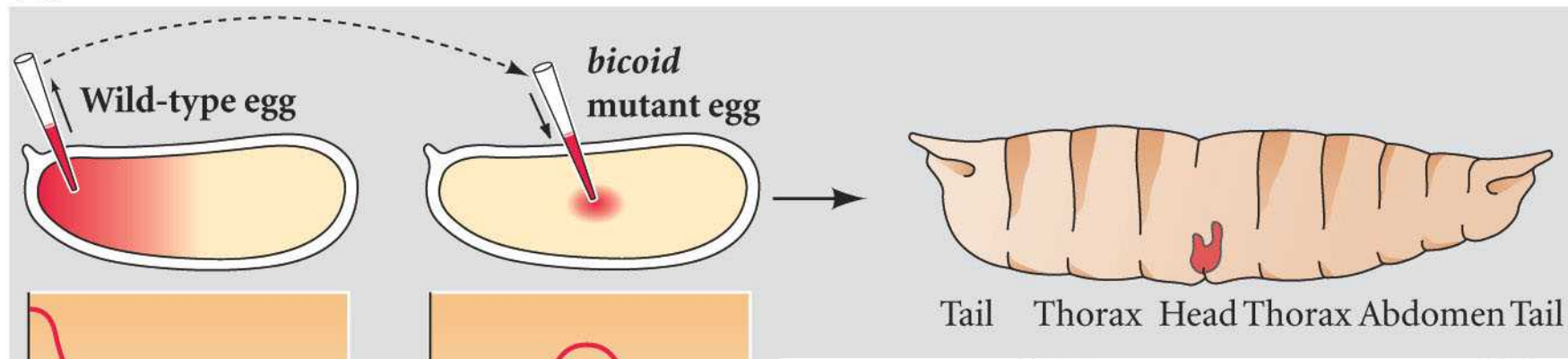


# Bicoid, morfógeno de cabeza

(B)

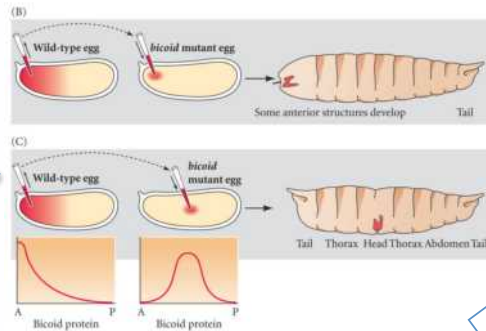
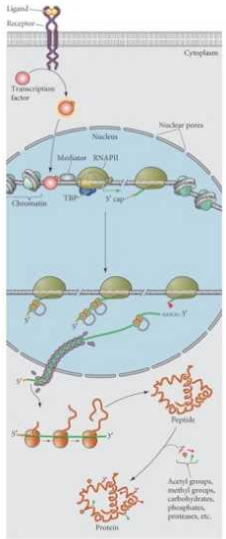


(C)



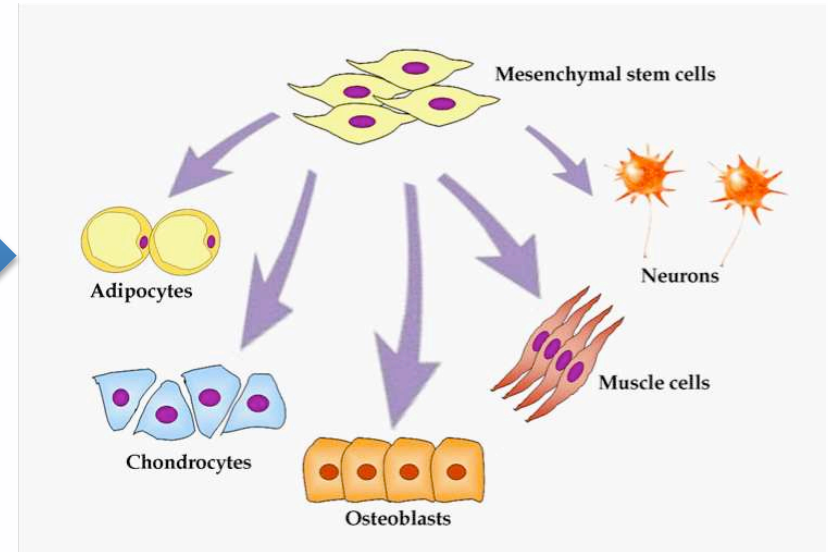
# Princípios gerais do desenvolvimento:

## A. Regulação gênica



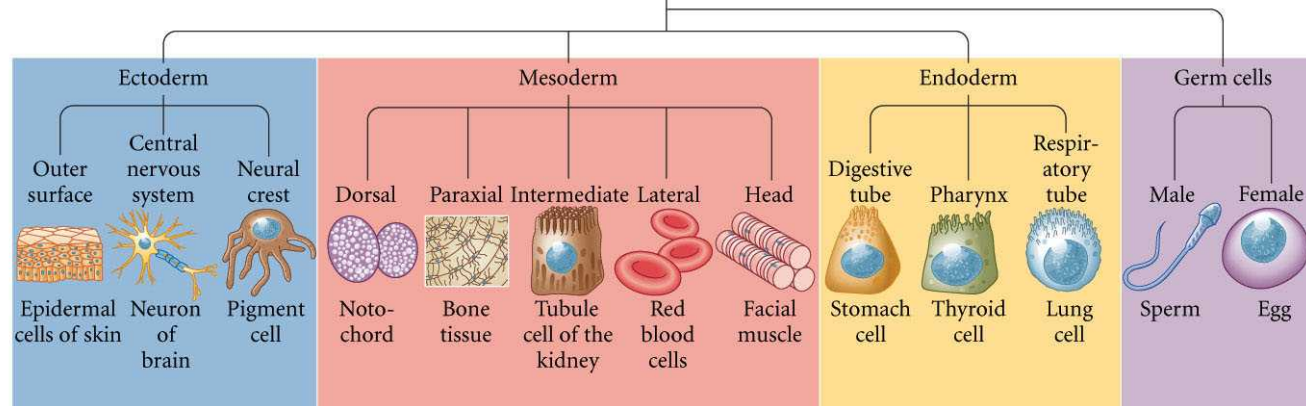
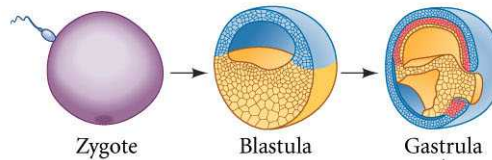
## B. Gradientes e morfógenos

## C. Especificação e diferenciação celular:



## C. Especificação e diferenciação celular embrionária:

- I. autônomo
- II. condicional
- III. (-syncicial)







# XX-XI Ideias Contemporâneas do desenvolvimento

## CONCLUSOES APOS A ATIVIDADE DE LEITURA DE MILESTONES....

- O desenvolvimento dos linagens celulares são progressivos e restritivos?
- Genes controlam o comportamento celular (só?)
- Regulação da expressão génica em células e tecidos (ncRNAs, modificações post-transcripcionais)
- Comunicação intercelular (ambiente celular)