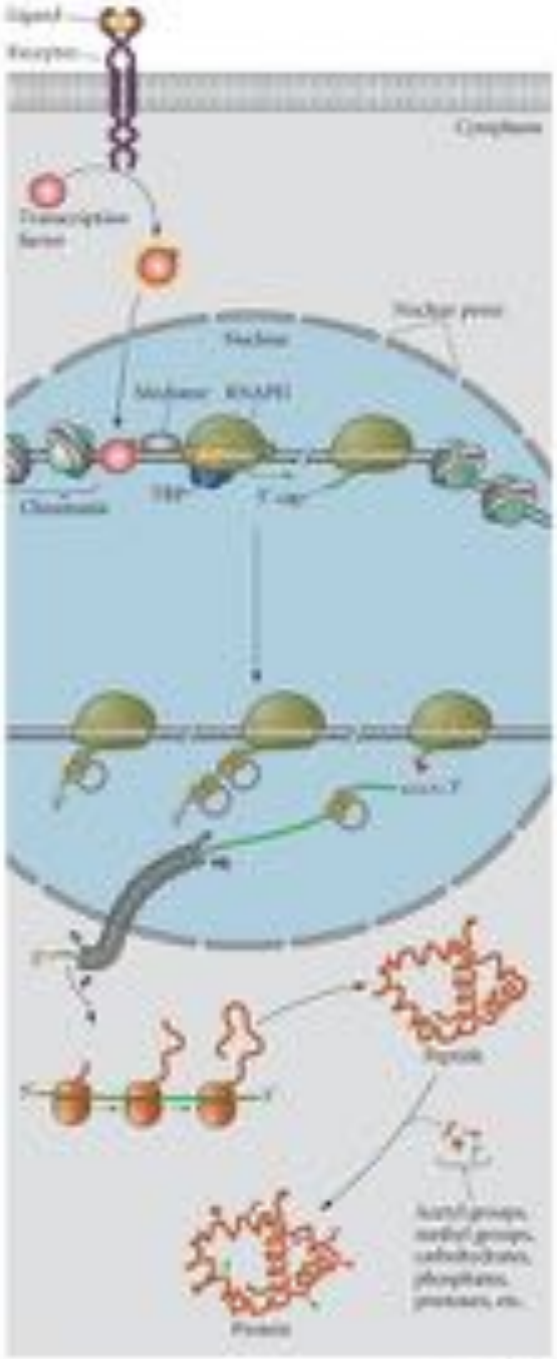
Regulação genética e as suas consequências no desenvolvimento

Expressão genética pode ser regulado em vários níveis:

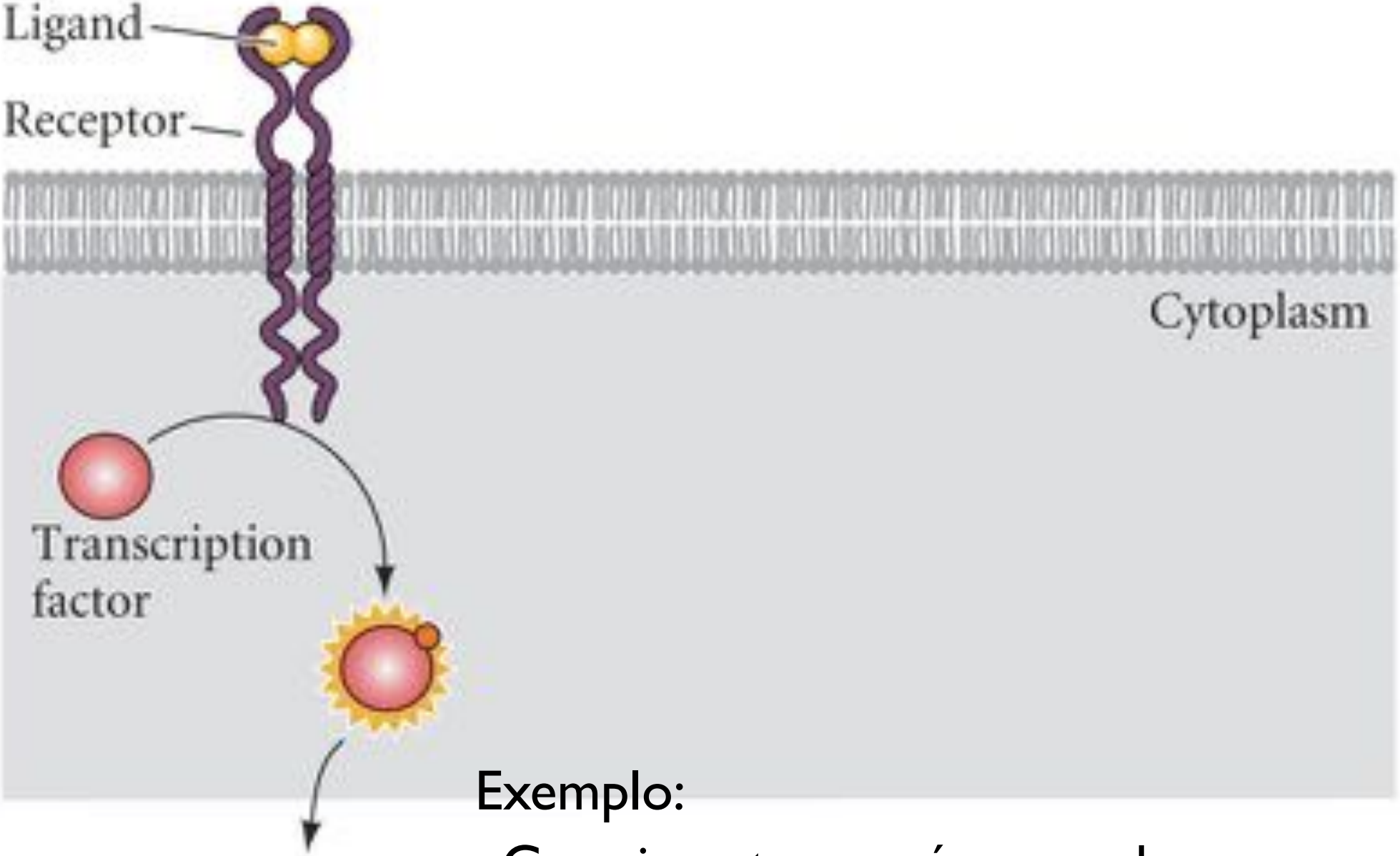
1) Ambiente extracelular e cascatas de sinalização

2) Transcripção



3) Traducção

1) Ambiente extracelular e cascatas de sinalização:

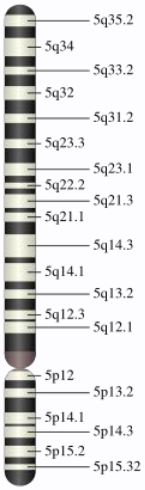


Exemplo:

Crescimento corpóreo em humanos

Crescimento corpóreo em humanos

Caso: Nanismo pituitário (Síndrome de Laron ou GHRD)



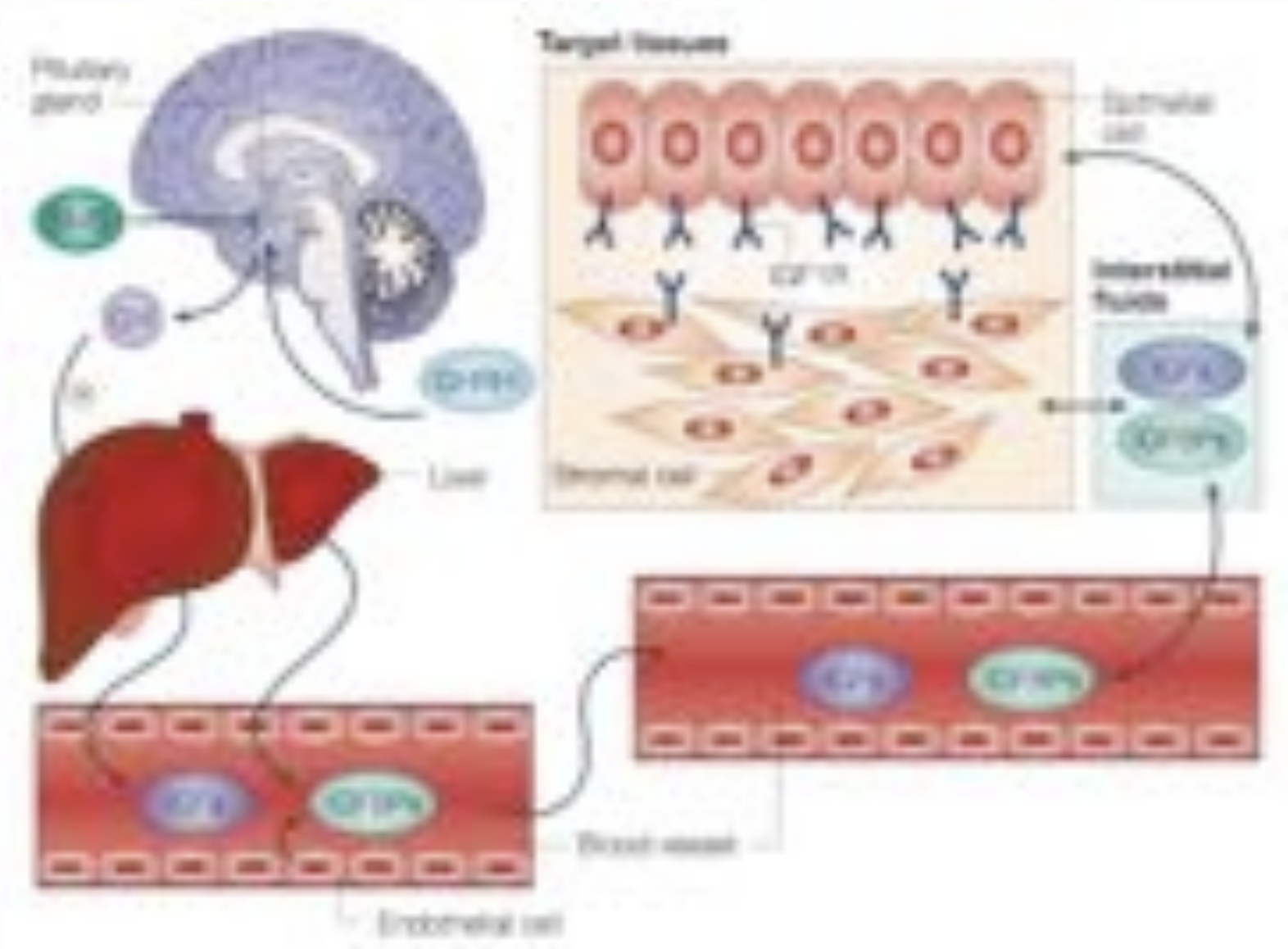
Rosenbloom et al. 1999

TABLE 1. Clinical features of GHRD

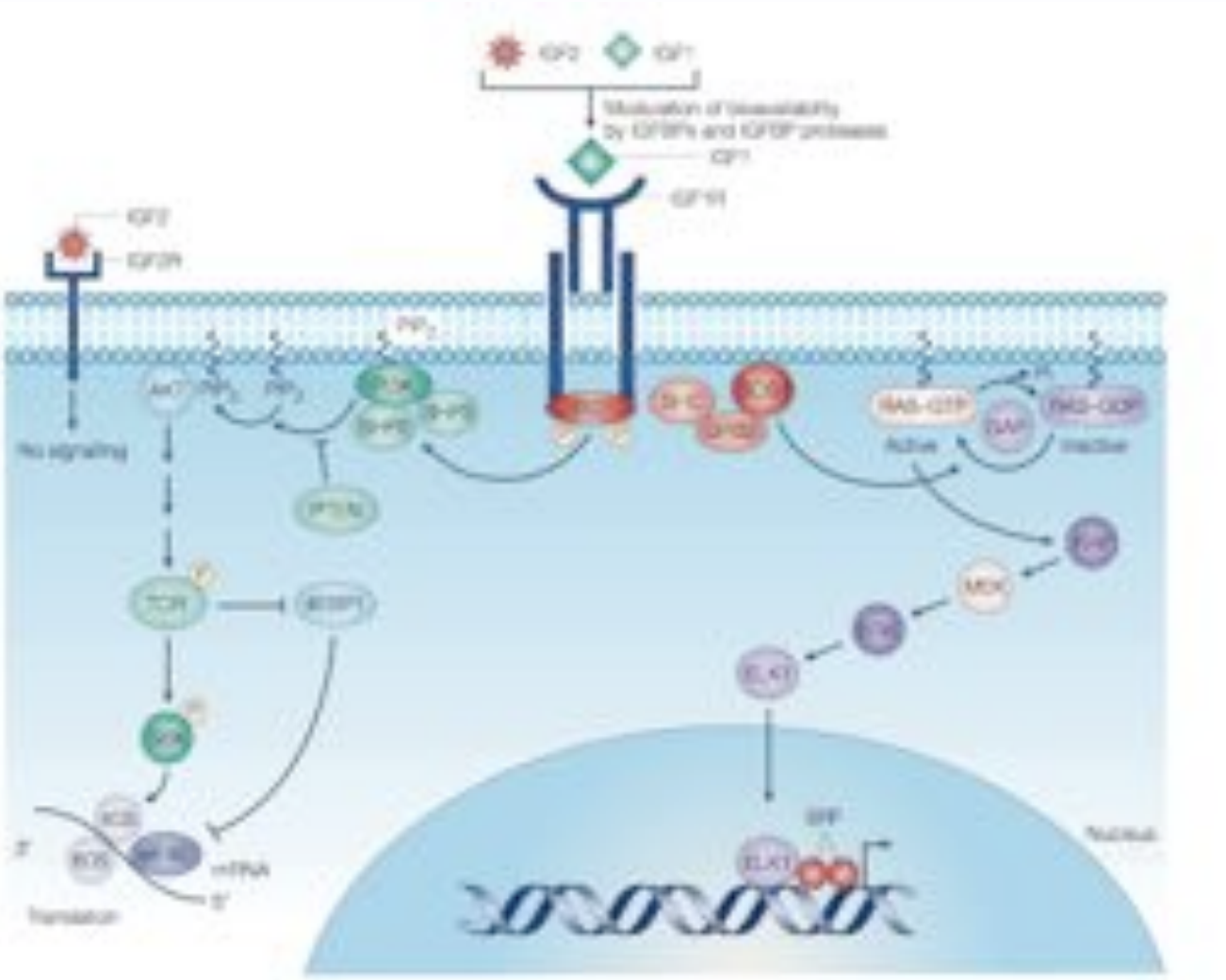
Growth
Birth weight–normal; birth length–usually normal[a]
Severe growth failure, from birth, with growth velocity ½ normal[a]
Height deviation correlates with (low) serum levels of IGF-I and IGFBP-3[b]
Delayed bone age, but advanced for height age[a]
Small (<10th percentile for height) hands or feet (70%)[a]
Body segment ratios normal for bone age in children, abnormal (reduced upper/lower, arms span) in adults[b]
Craniofacial characteristics
Sparse hair before age 7 (70%); frontal temporal hairline recession all ages[a]
Prominent forehead
Head size more normal than stature with impression of large head[b]
Hypoplastic nasal bridge, shallow orbits
Decreased vertical dimension of face[a]
"Setting sun sign" under 10 yr of age (25%)[a]
Blue sclerae[b]
Prolonged retention of primary dentition with decay; normal, crowded permanent teeth
Sculpted chin[b]
Unilateral ptosis, facial asymmetry (15%)[b]
Musculoskeletal/body composition
Hypomuscularity with delay in walking (70%)[a]
Hip dysplasia: avascular necrosis of femoral head (25%)[b]
High pitched voices in all children, 90% adults[a]
Thin, prematurely aged skin
Limited elbow extensibility (acquired, 85% after age 5 yr)[b]
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[b]
Osteopenia[a]
Metabolic
Hypoglycemia (fasting)
Increased cholesterol and LDL-C[b]
Decreased sweating
Sexual development
Small penis in childhood; normal genital growth with adolescence
Delayed puberty (50%) in both sexes[a]
Normal reproductive function[a]

[a] Observations expanded, modified, or quantified in the Ecuadorean cohort.
[b] New observations in the Ecuadorean cohort.

Caso: Nanismo pituitário (Síndrome de Laron ó GHRD)



Pollak et al. 2004



Pollak et al. 2004

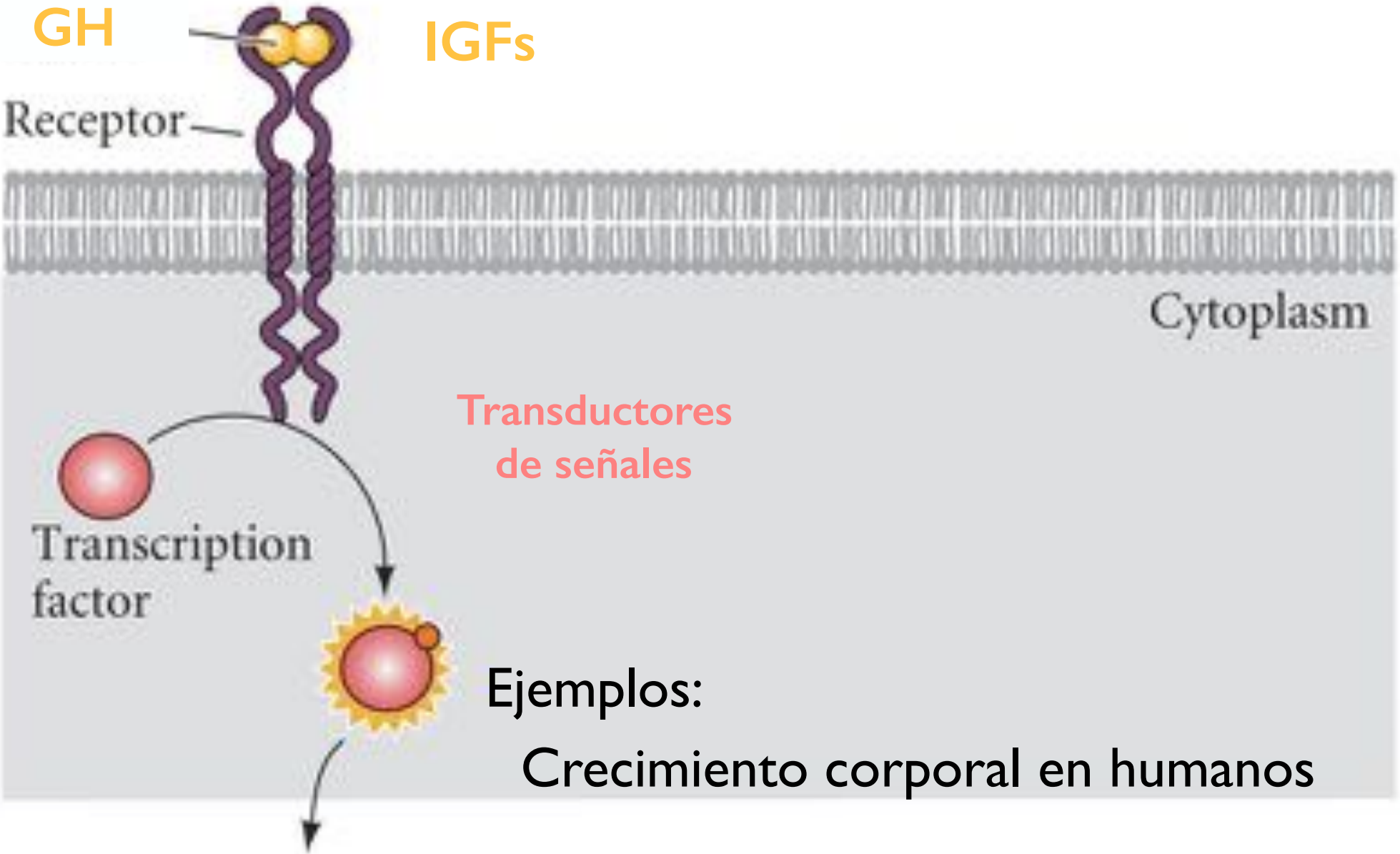
Se você fosse o médico,
o qual tratamento você
aplicaria à seus
pacientes?

Tratamento com IGF-I

Paciente de 18 años, seis meses
después de tratamiento

Rosenbloom et al. 1999

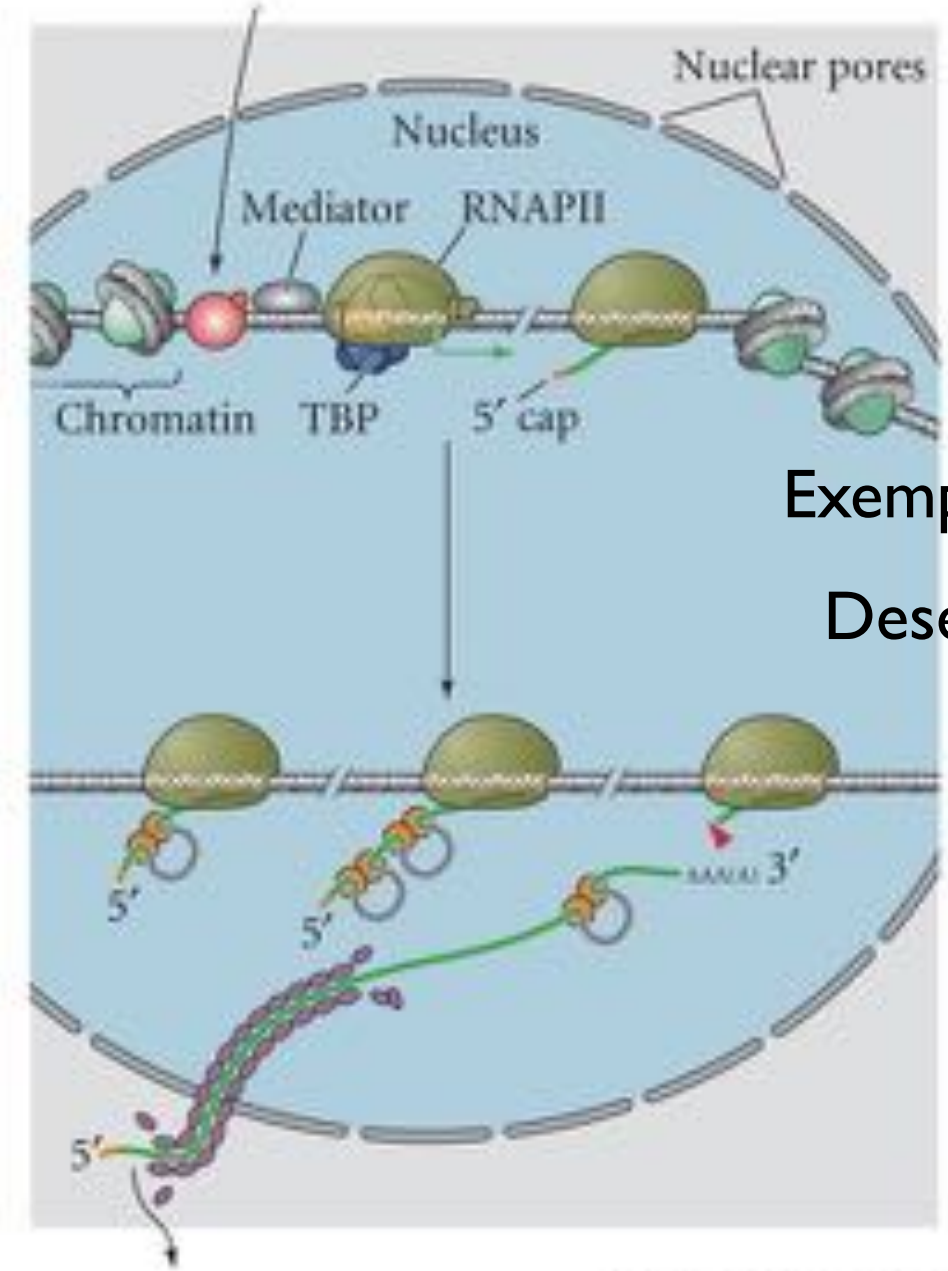
1) Resumo sinalização:



Ejemplos:

Crecimiento corporal en humanos

2) Transcripção



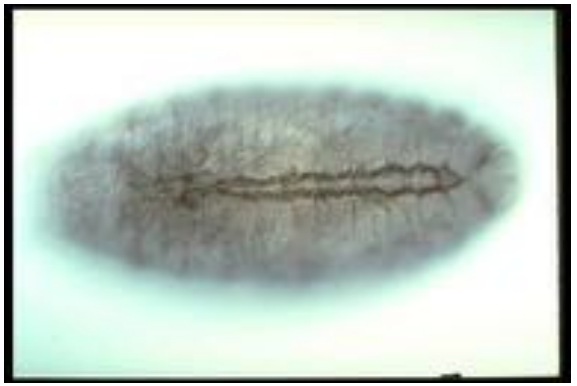
Exemplo:

Desenvolvimento do coração

DEVELOPMENTAL BIOLOGY, Seventh Edition, Figure 6.35 (Part 2)


FRED R. HAMLIN'S MUSICAL EXTRAVAGANZA
THE WIZARD OF OZ
· THE TIN MAN ·

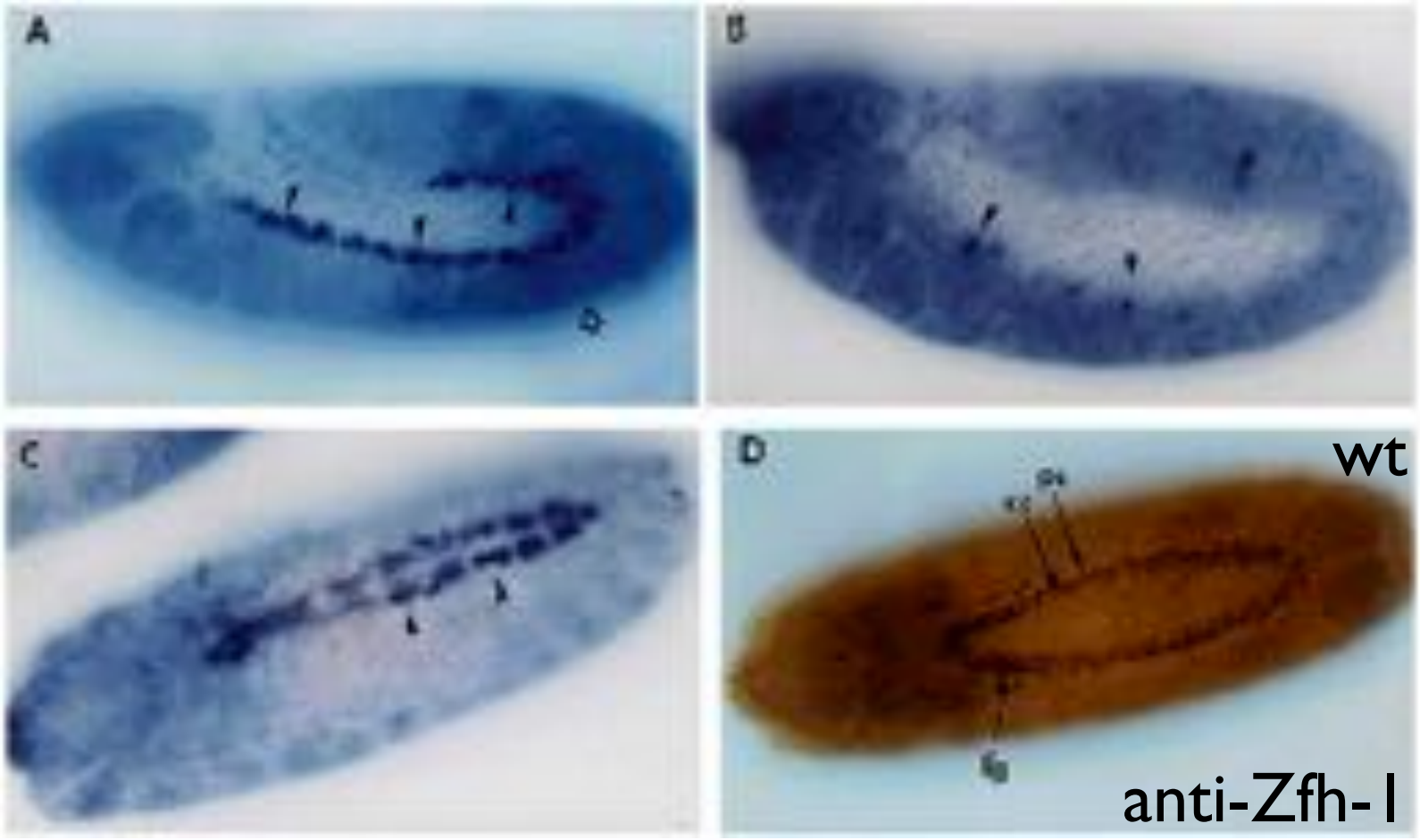
Drosophila:



tinman (tin RNA)

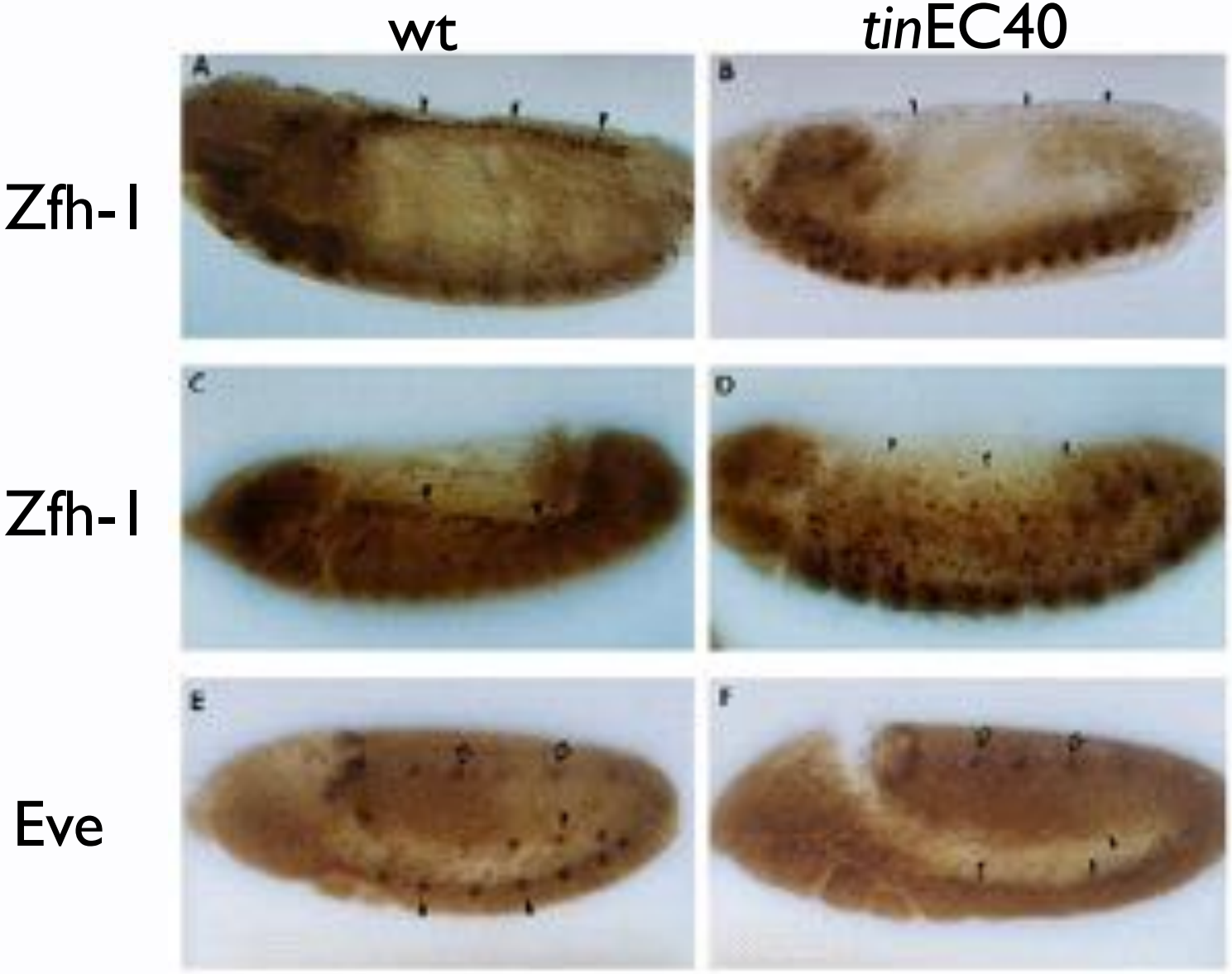
wt

*tin*EC40



Bodmer 1993

desenvolvimento do coração

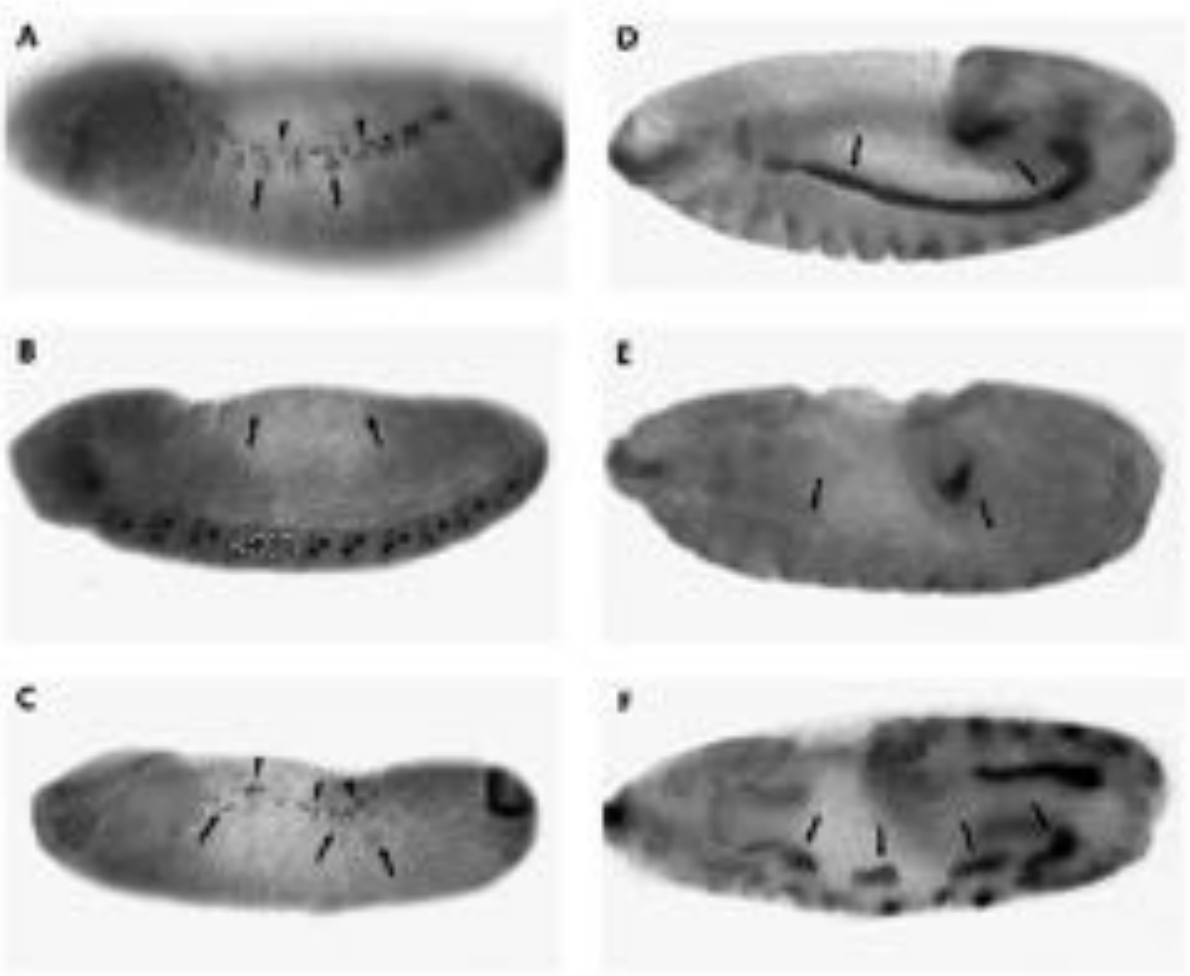


rescate do mutante *tin*

wt

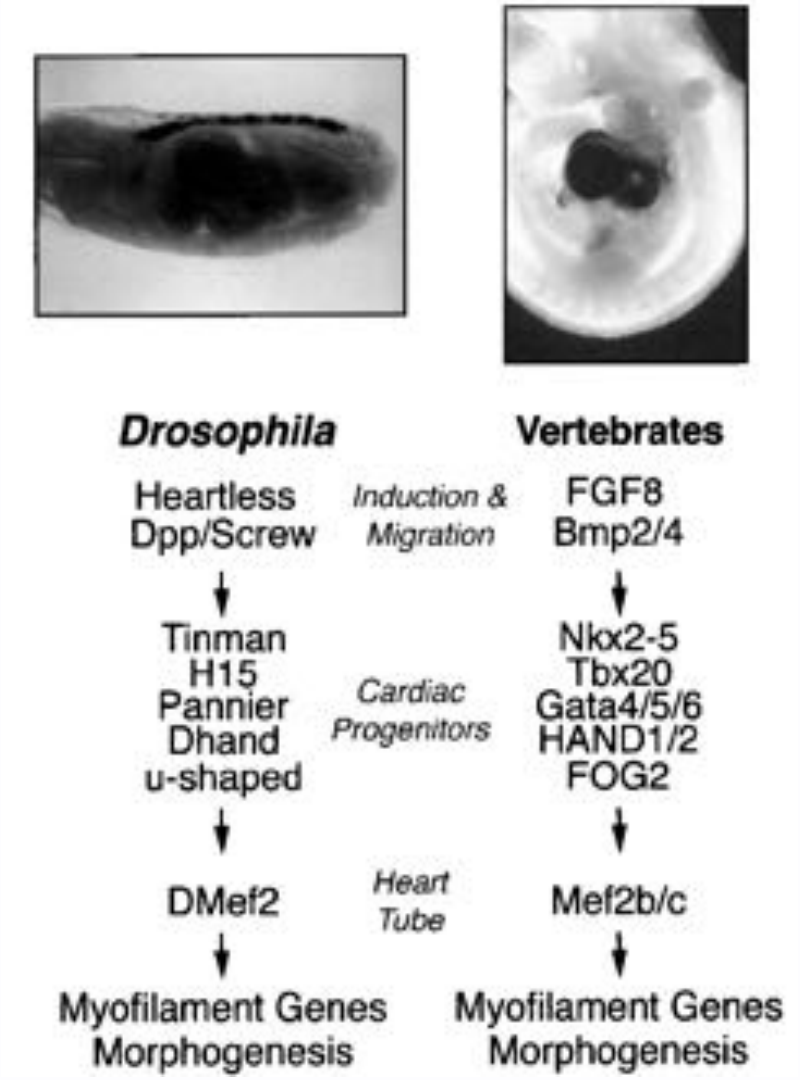
hs*tin9A* *control*

hs*tin9A*



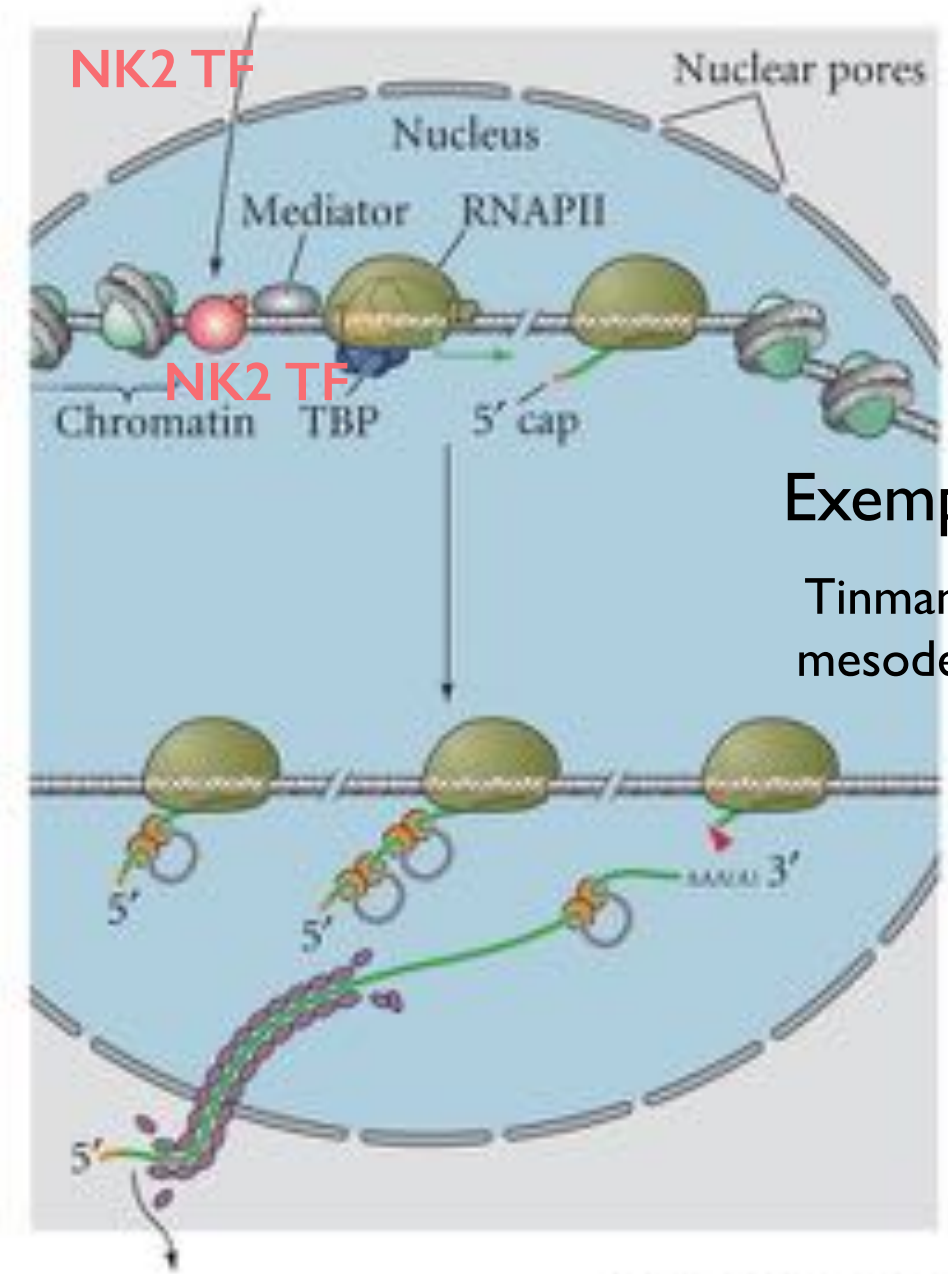
(anti Eve)

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



Prall et al. 2002

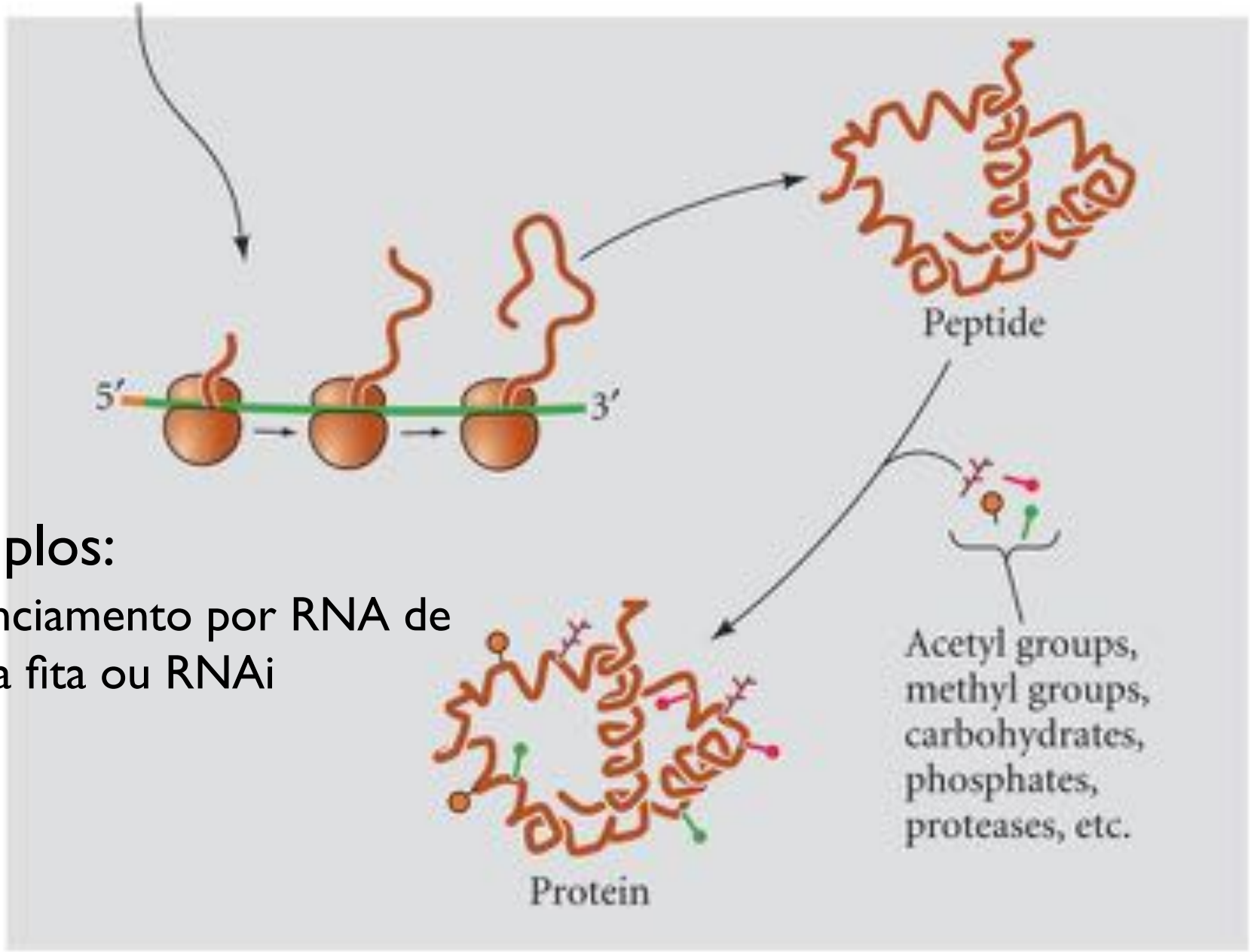
2) Resumo transcrição:



Exemplo:

Tinman é necessário para a formação de mesoderme e coração.

3) Tradução

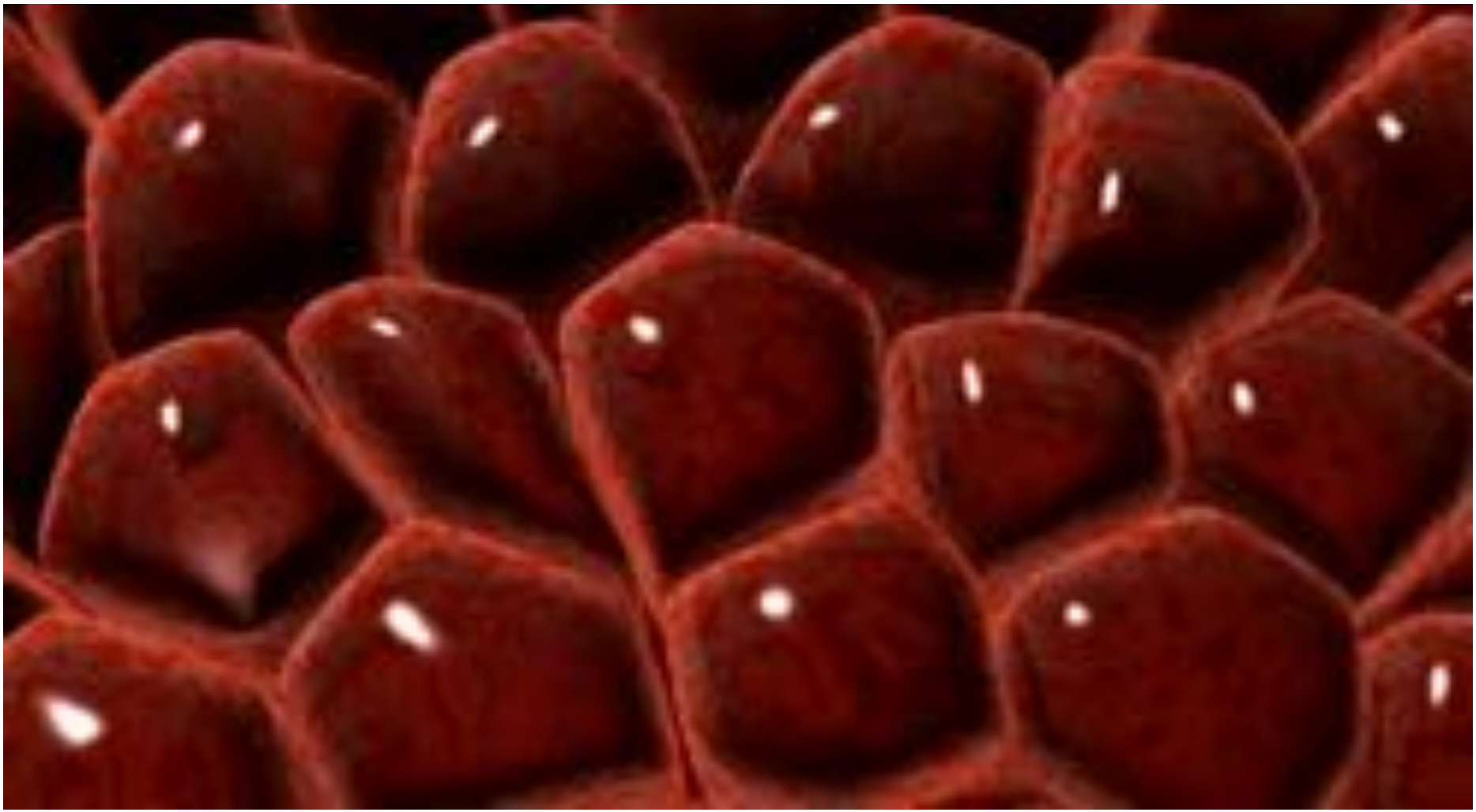


Exemplos:

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 descubrem silenciamento por RNAi (1998).



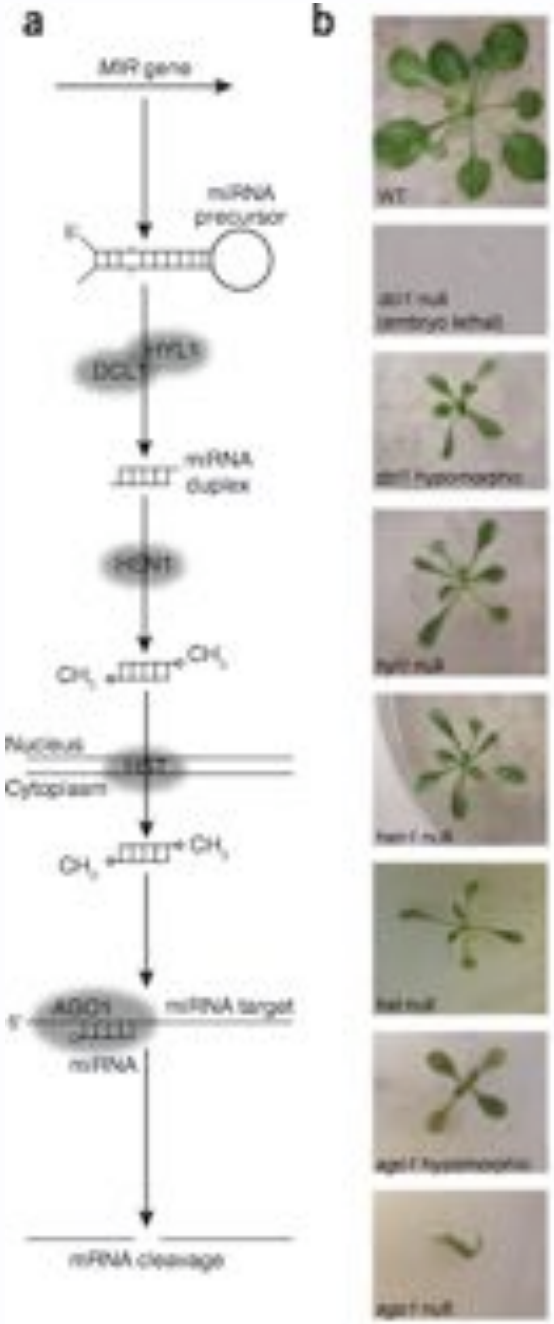
Silenciamento genético por RNA de cadeia dupla (miRNA, siRNA, RNAi)

Craig Mello
University of Massachusetts

Andrew Fire
Stanford University

Nobel 2006

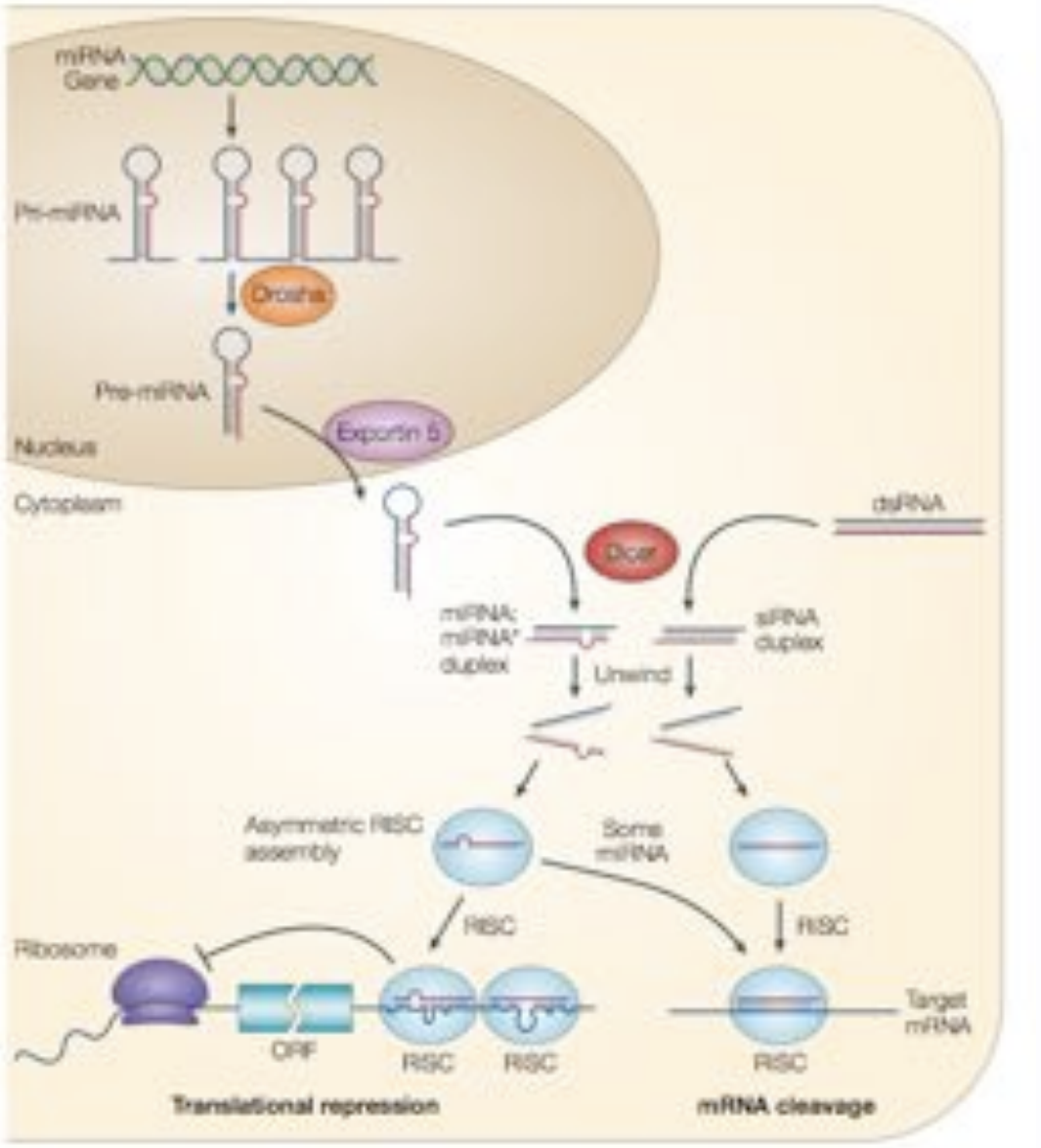
Disrupção do silenciamento por miRNAs em plantas



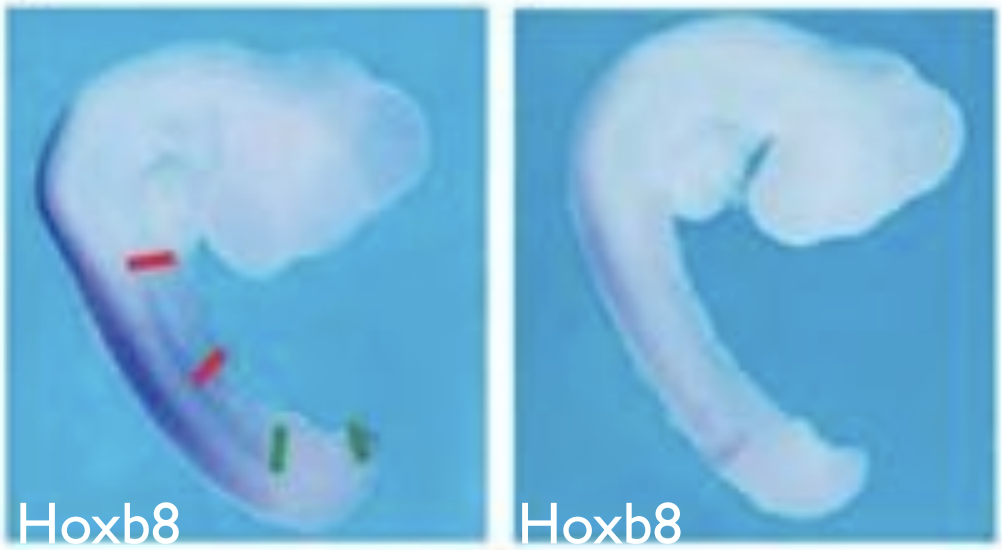
Mallory & Vaucheret, 2006

Acção dos RNAs menores em animais

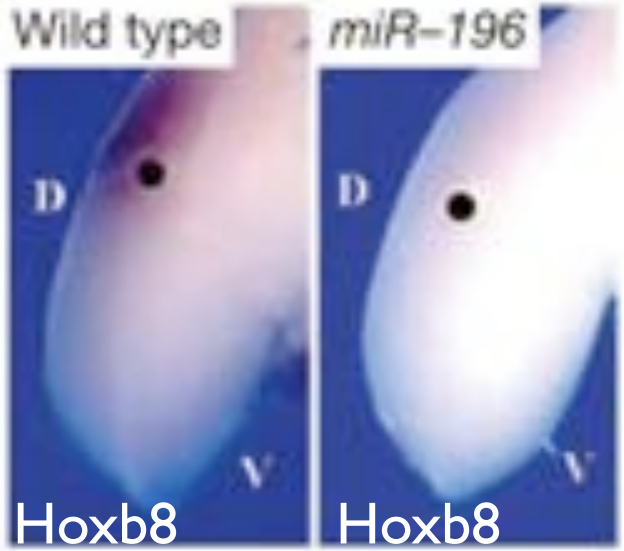
He & Hannon, 2004



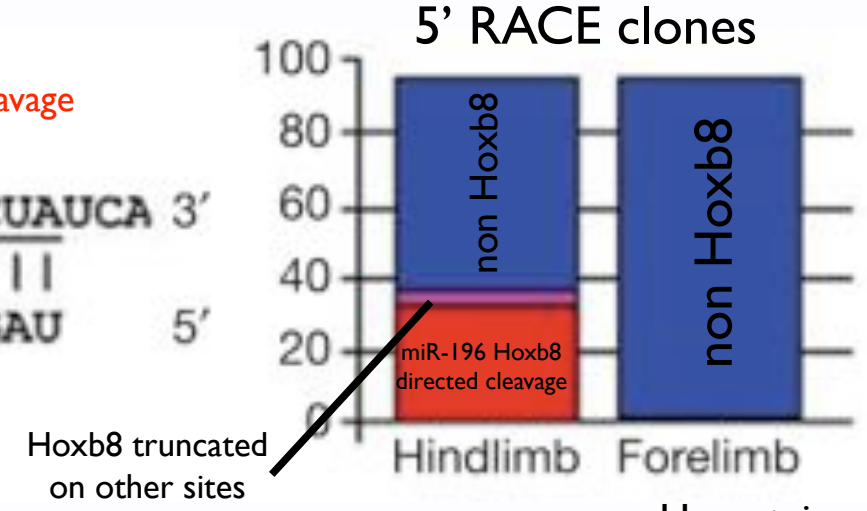
miR-196 regula Hoxb8 no desenvolvimento dos membros em vertebrados



embrião de galinha (st. 16)



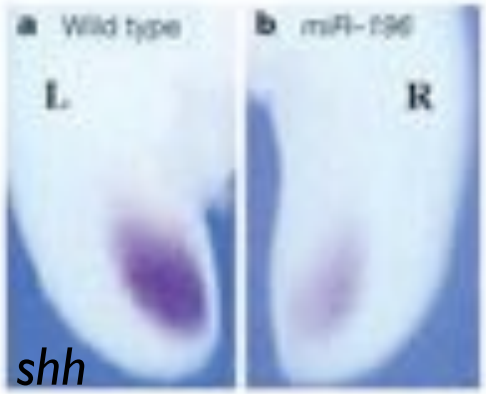
extremidade anterior de galinha (st. 22)

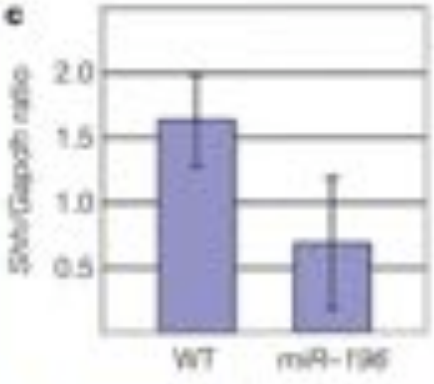


Hornstein et al. 2005

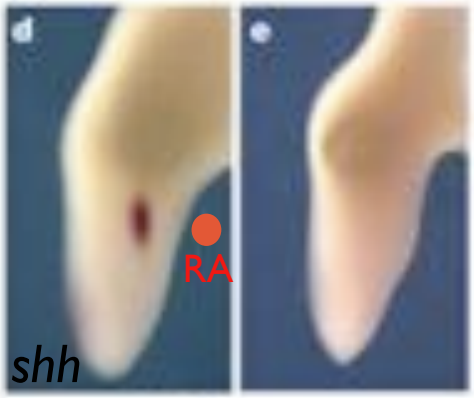
miR-196 regula Shh no desenvolvimento dos membros em vertebrados

membro anterior

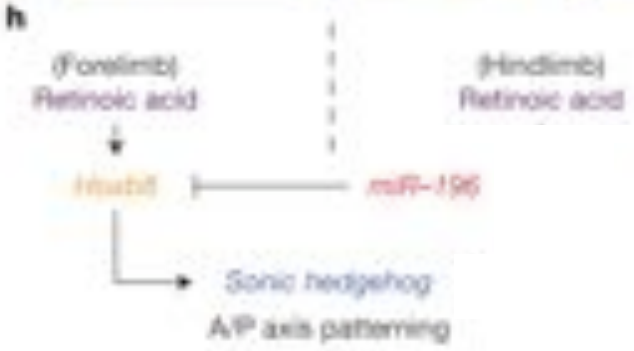




membro anterior



Modelo de regulação:



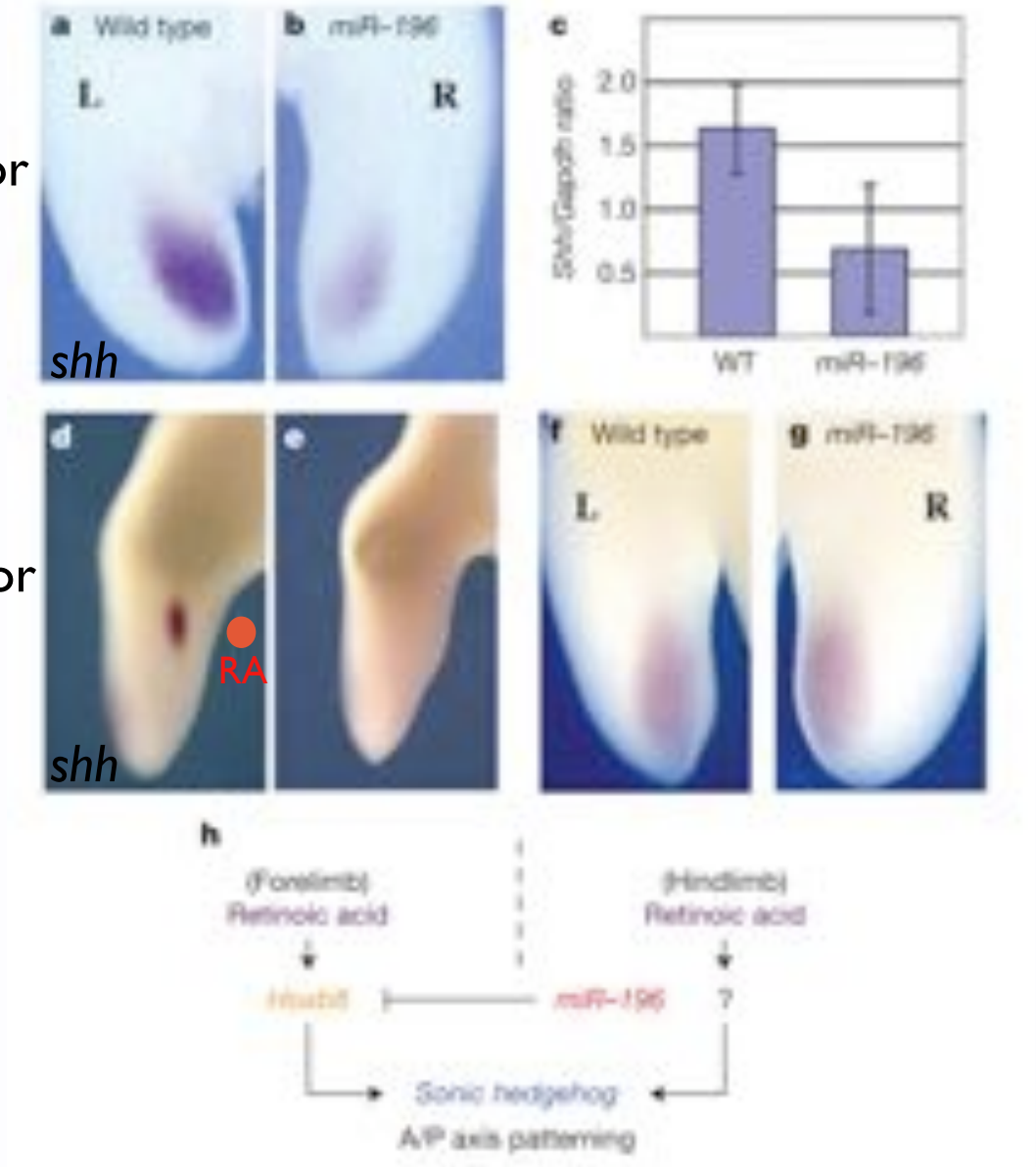
Hornstein et al. 2005

miR-196 regula Shh no desenvolvimento dos membros em vertebrados

membro anterior

membro anterior

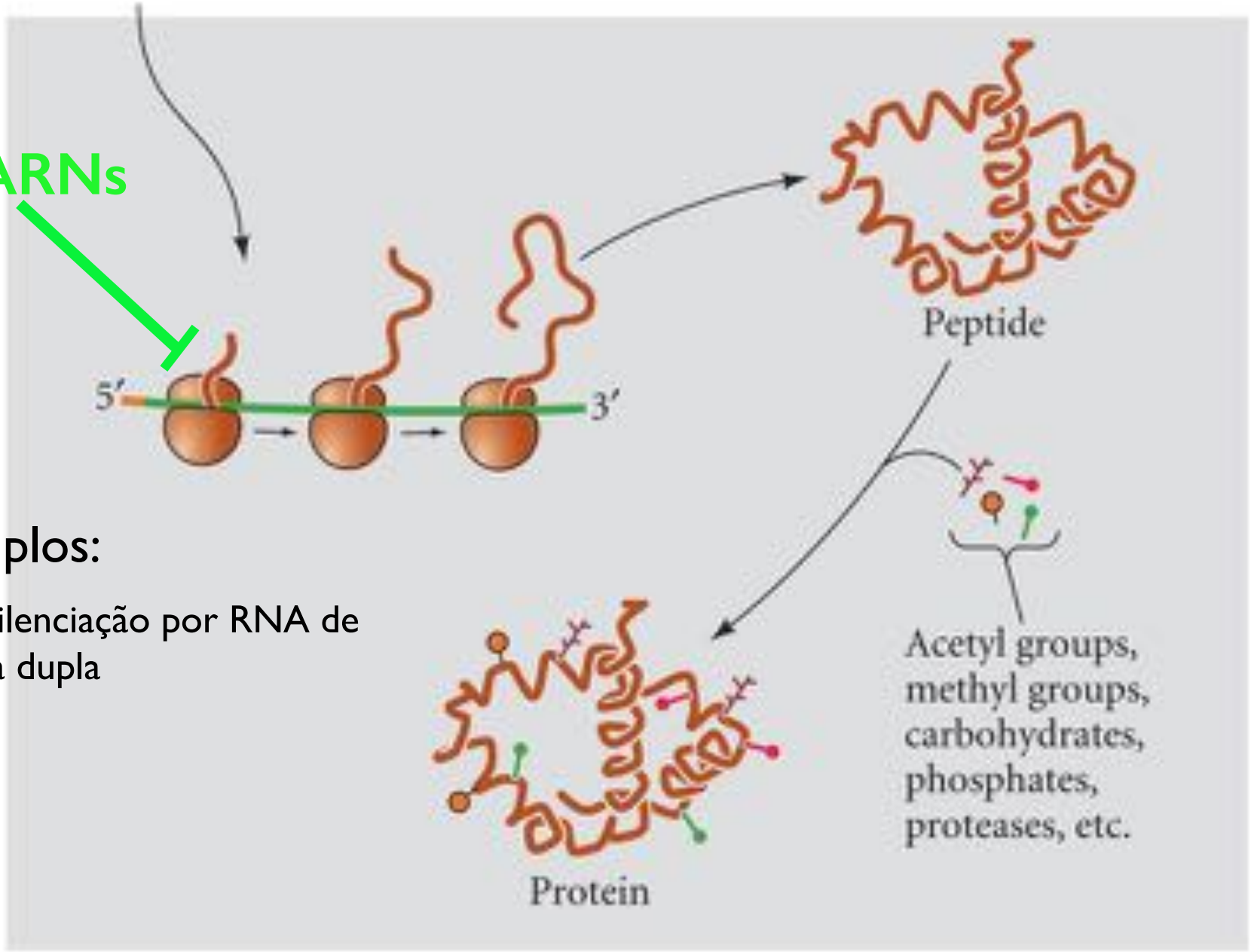
membro posterior



Modelo de regulação:

Hornstein et al. 2005

3) Tradução



Exemplos:

3.1) Silenciação por RNA de cadeia dupla

Expressão génética pode ser regulada a vários níveis:

1) Ambiente extracelular e cascadas de sinalização

sinais endócrinas: IGFIR

2) Transcrição

fatores de transcrição: Tinman

3) Tradução

disrupção de tradução por miRNAs

DEVELOPMENTAL BIOLOGY, Seventh Edition, Figure 5.35 Sinauer Associates, Inc.