DIFERENCIACIÓN CELULAR

ASPECTOS GENERALES

MECANISMOS CELULARES Y MOLECULARES



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EL PROCESO DE FORMACION DE ORGANOS Y TEJIDOS IMPLICA TRES PROCESOS BASICOS CONTROLADOS POR ESTIMULOS EXTRACELULARES

PROLIFERACIÓN CELULAR

DIFERENCIACIÓN CELULAR

MUERTE CELULAR

DIFERENCIACIÓN CELULAR

DEFINICIÓN CONCEPTUAL:

PROCESO MEDIANTE EL CUAL UNA CELULA ADQUIERE CARACTERISTICAS MORFOLÓGICAS Y FUNCIONALES PARTICULARES

DEFINICIÓN OPERACIONAL:

COMO PODEMOS DEFINIR UNA CELULA DIFERENCIADA?

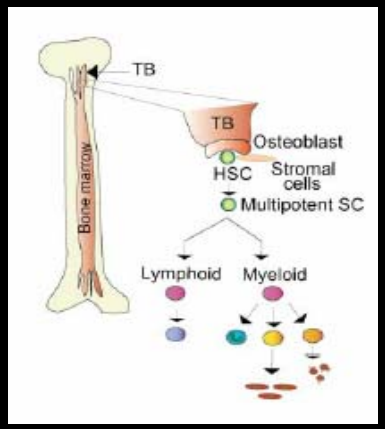
PODEMOS DEFINIR UNA CELULA DIFERENCIADA EN FORMA OPERACIONAL

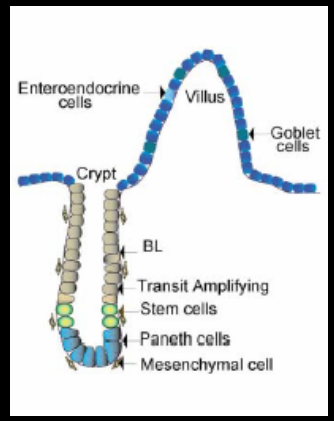
1.- CARACTERISTICAS CELULARES O MORFOLÓGICAS
2.- CARACTERISTICAS MOLECULARES (EXPRESIÓN DIFERENCIAL DE GENES)

Diferenciación celular

- Desarrollo embrionario y postnatal

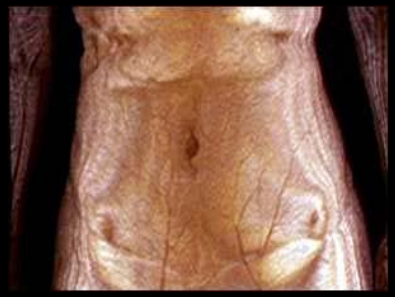
- Renovación de tejidos homeostasis

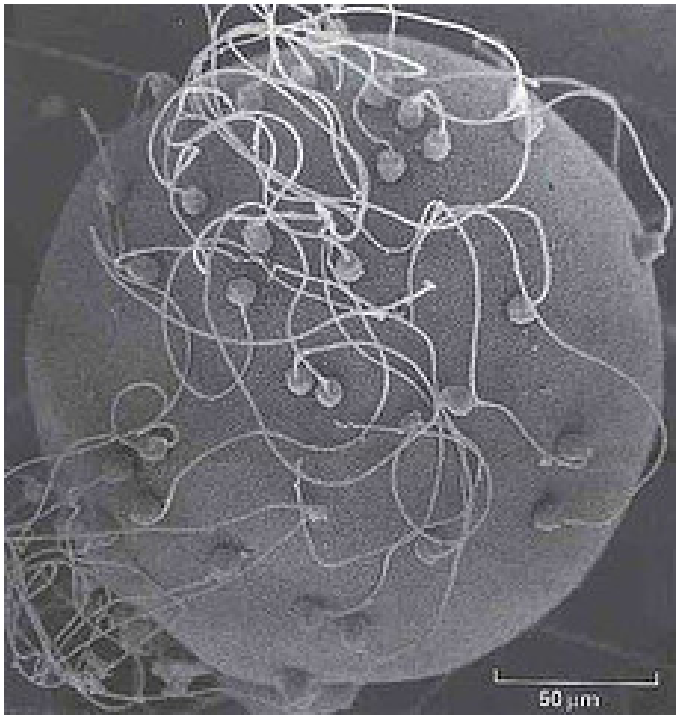


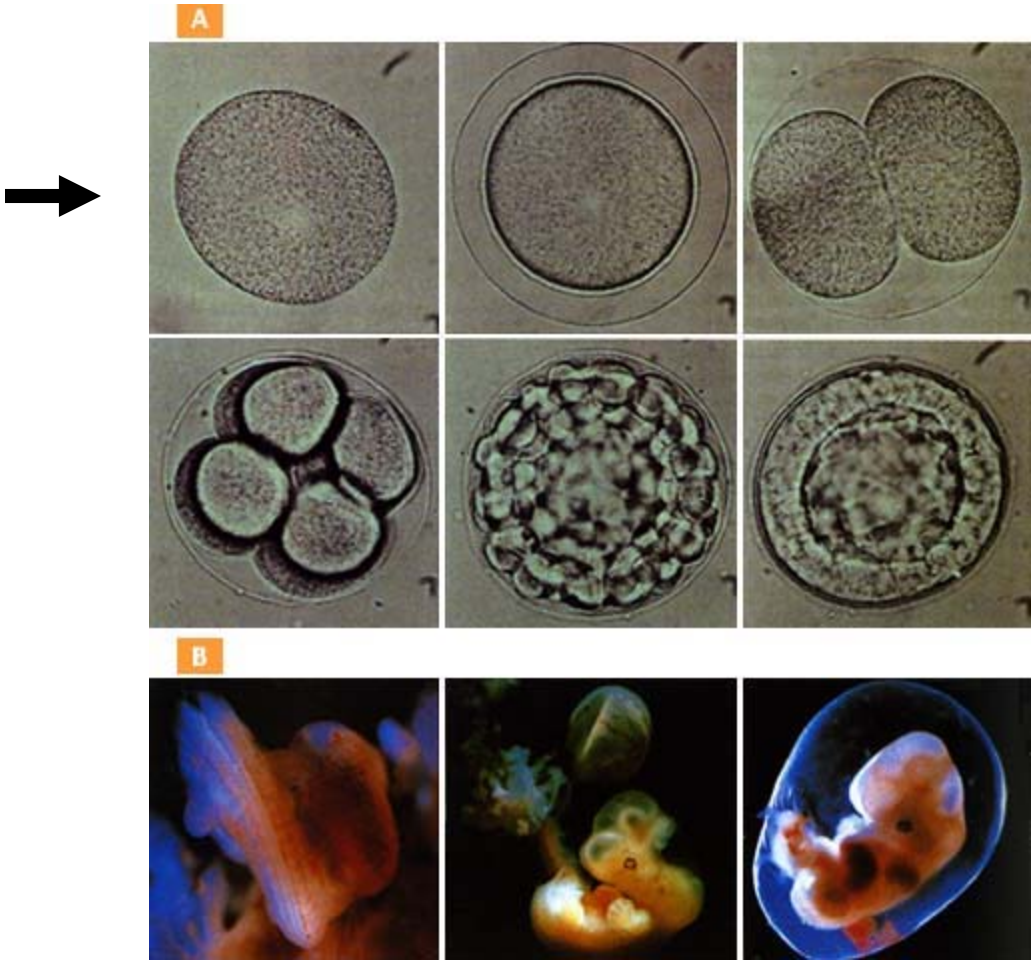


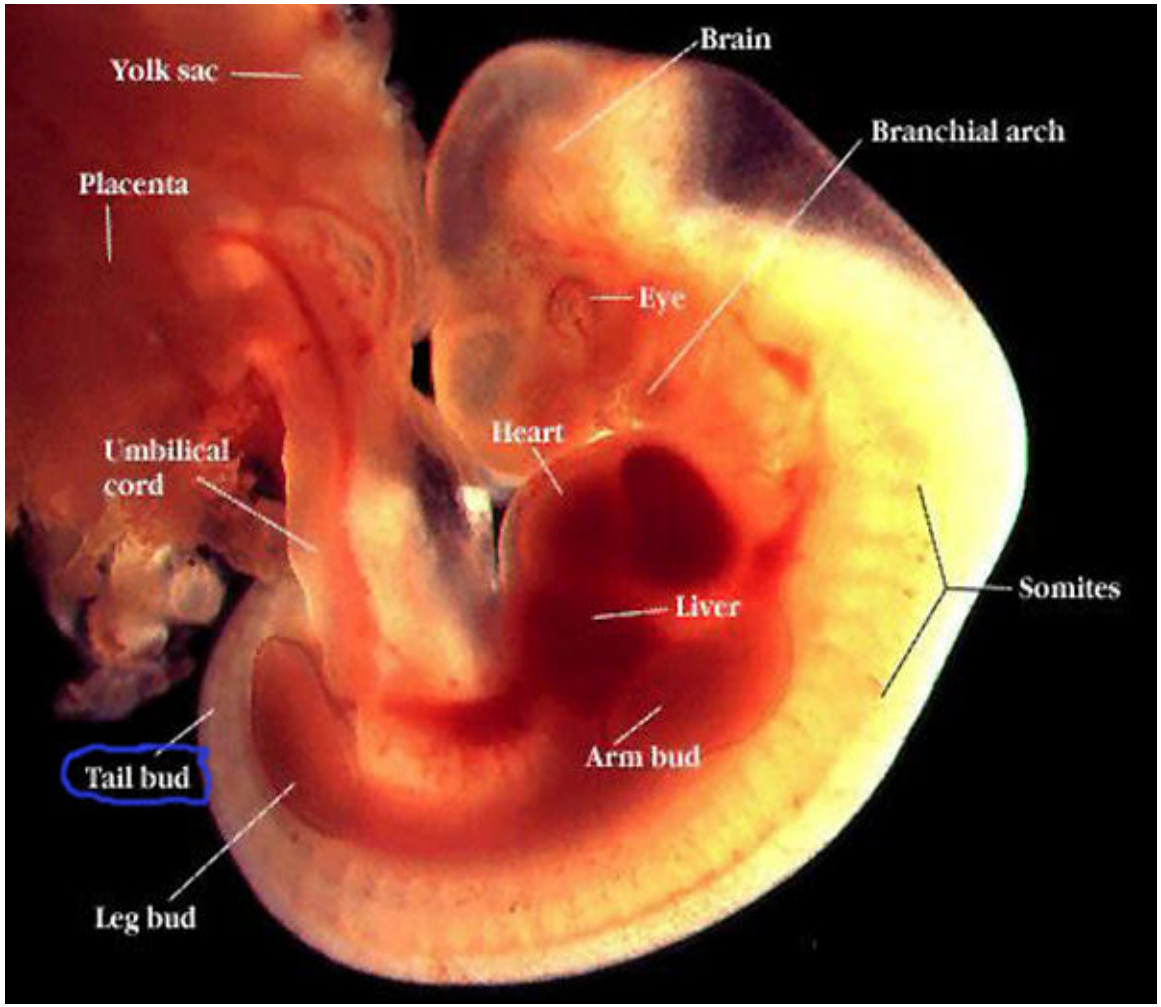
- Reparación de tejidos daño

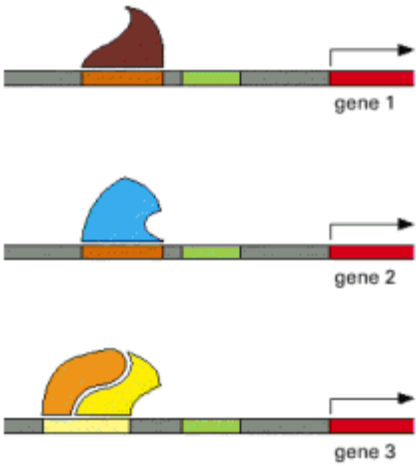
- Ingeniería de tejidos



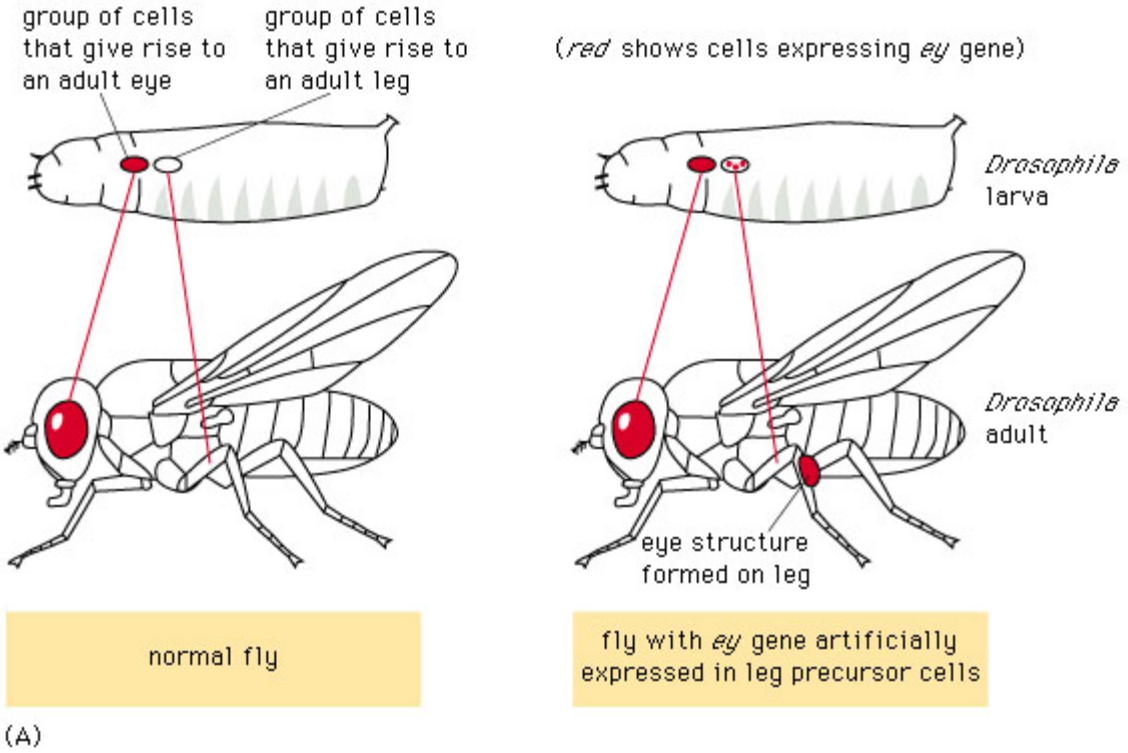

50 µm


A
B


Yolk sac
Brain
Branchial arch
Placenta
Eye
Heart
Umbilical cord
Somites
Liver
Arm bud
Tail bud
Leg bud


gene 1
gene 2
gene 3

ey




(B)

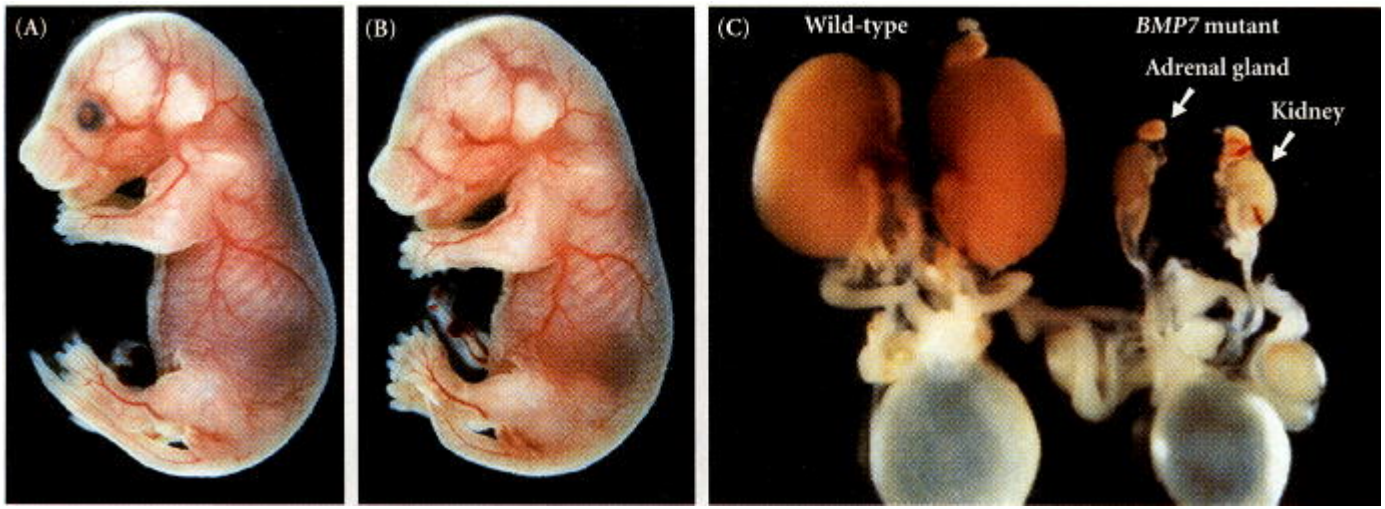
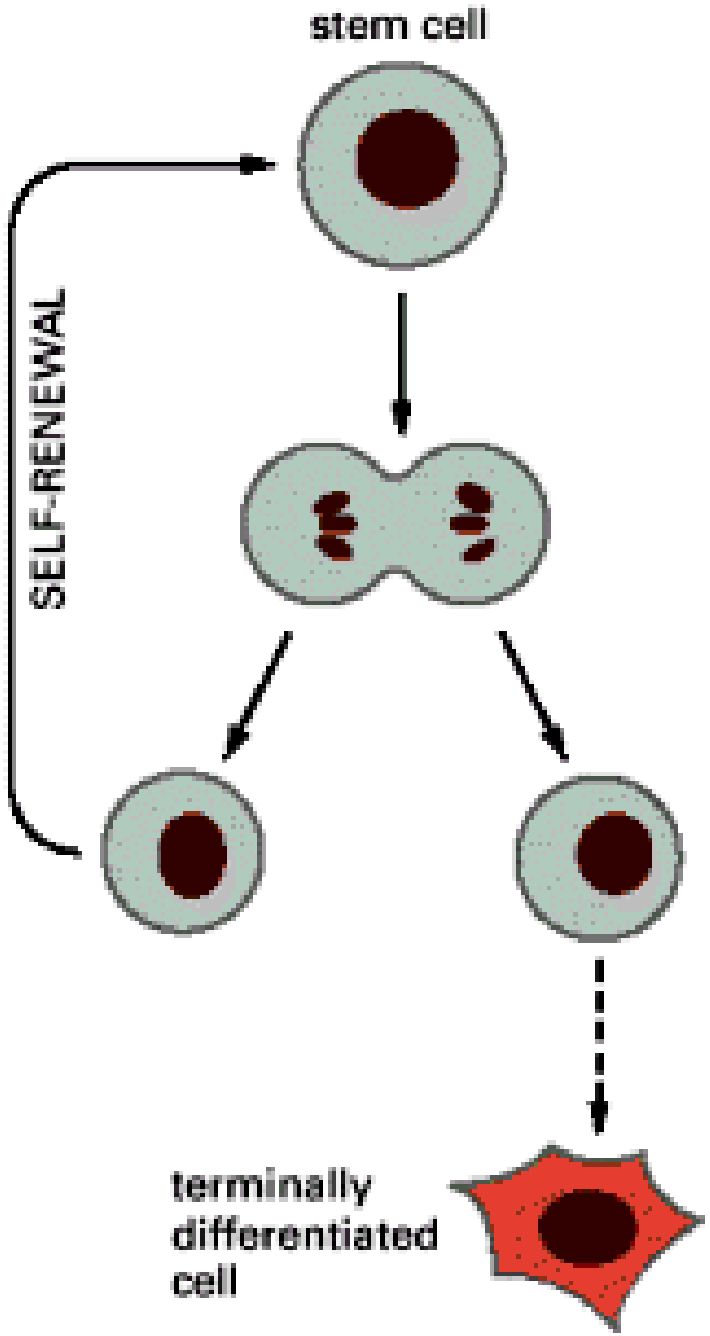


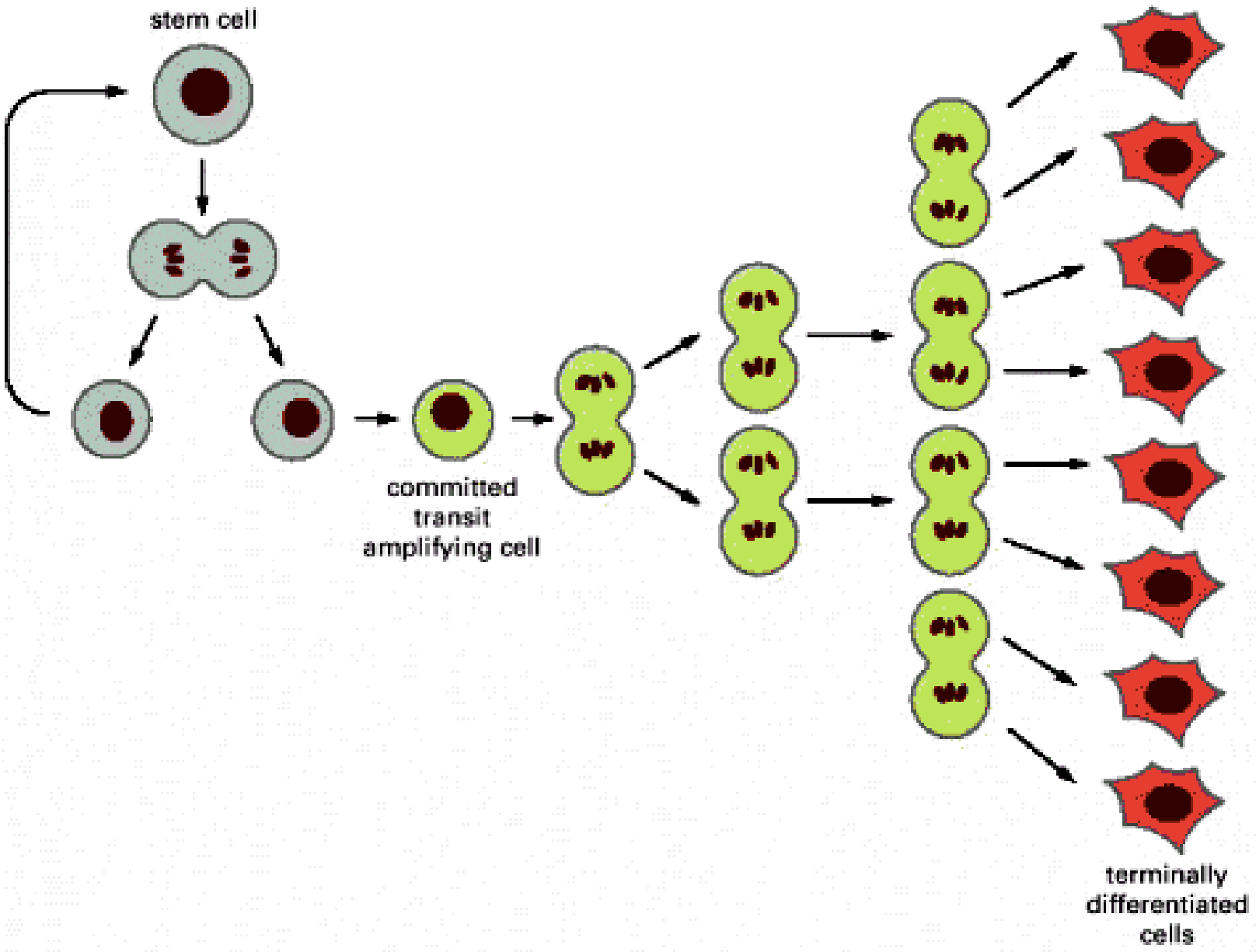
Figure 4.21. Morphological analysis of *BMP7* knockout mice. A wild-type (A) and a homozygous BMP7-deficient mouse (B) at day 17 of their 21-day gestation. The BMP7-deficient mouse lacks eyes. The kidneys of these mice at day 19 of gestation are shown in (C). The kidney of the BMP7-deficient mouse is severely atrophied. Microscopic sections revealed the death of the cells that would otherwise have formed the nephrons. (From Dudley et al. 1995; photographs courtesy of E. Robertson.)

TEJIDOS EN RENOVACIÓN

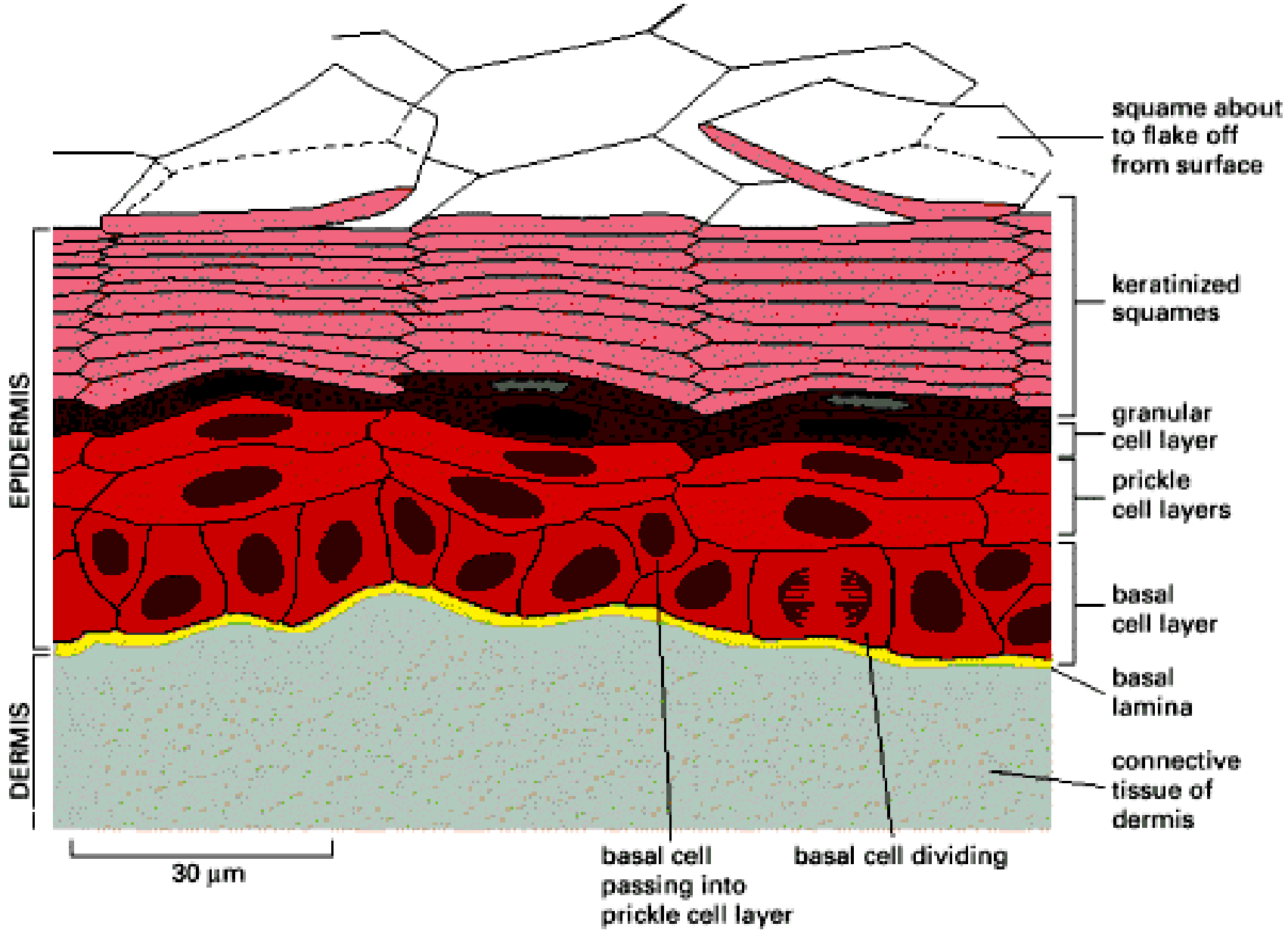
STEM CELL - CÉLULAS TRONCALES

MONOPOTENCIALES

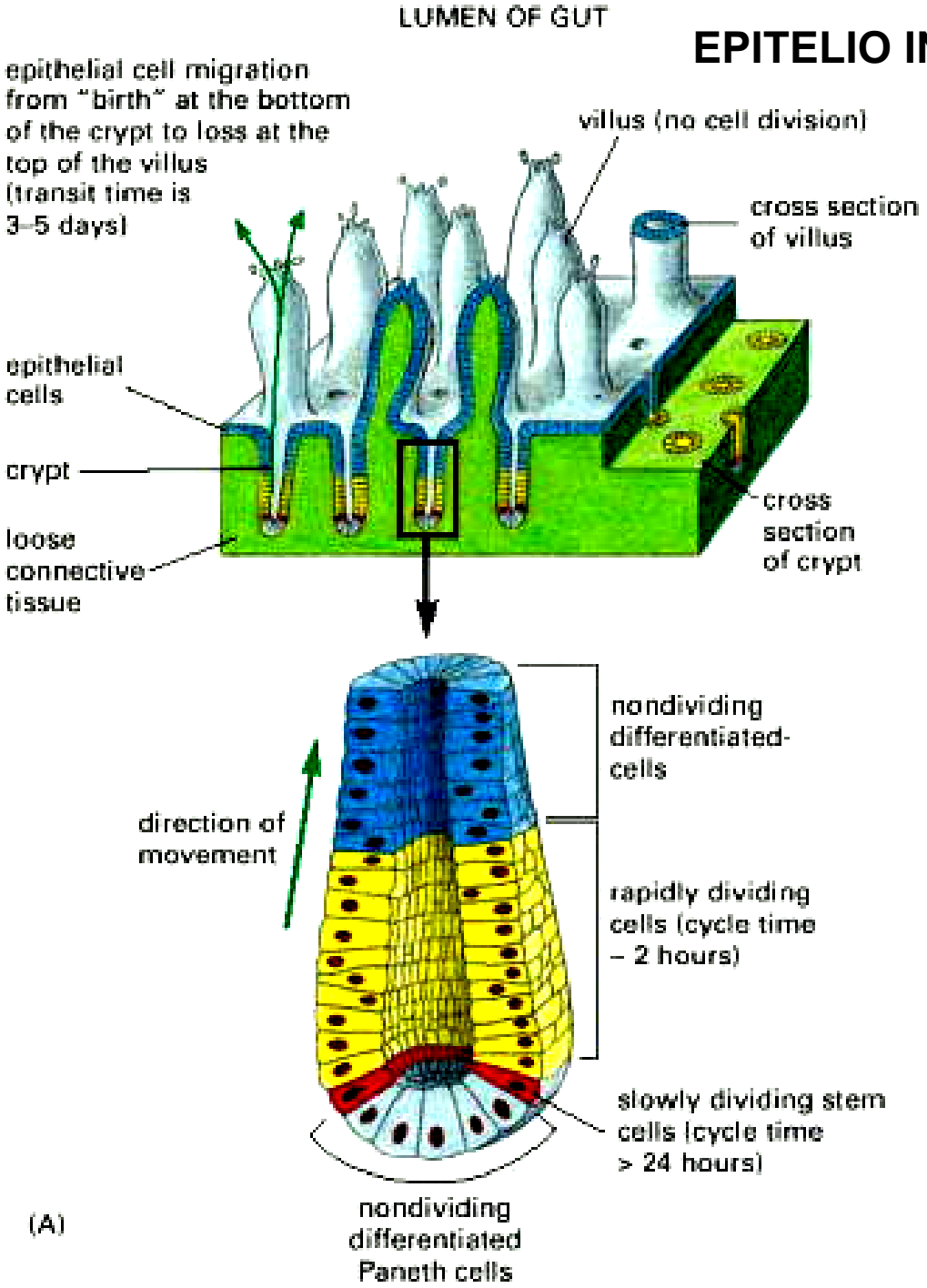

stem cell
SELF-RENEWAL
terminally
differentiated
cell

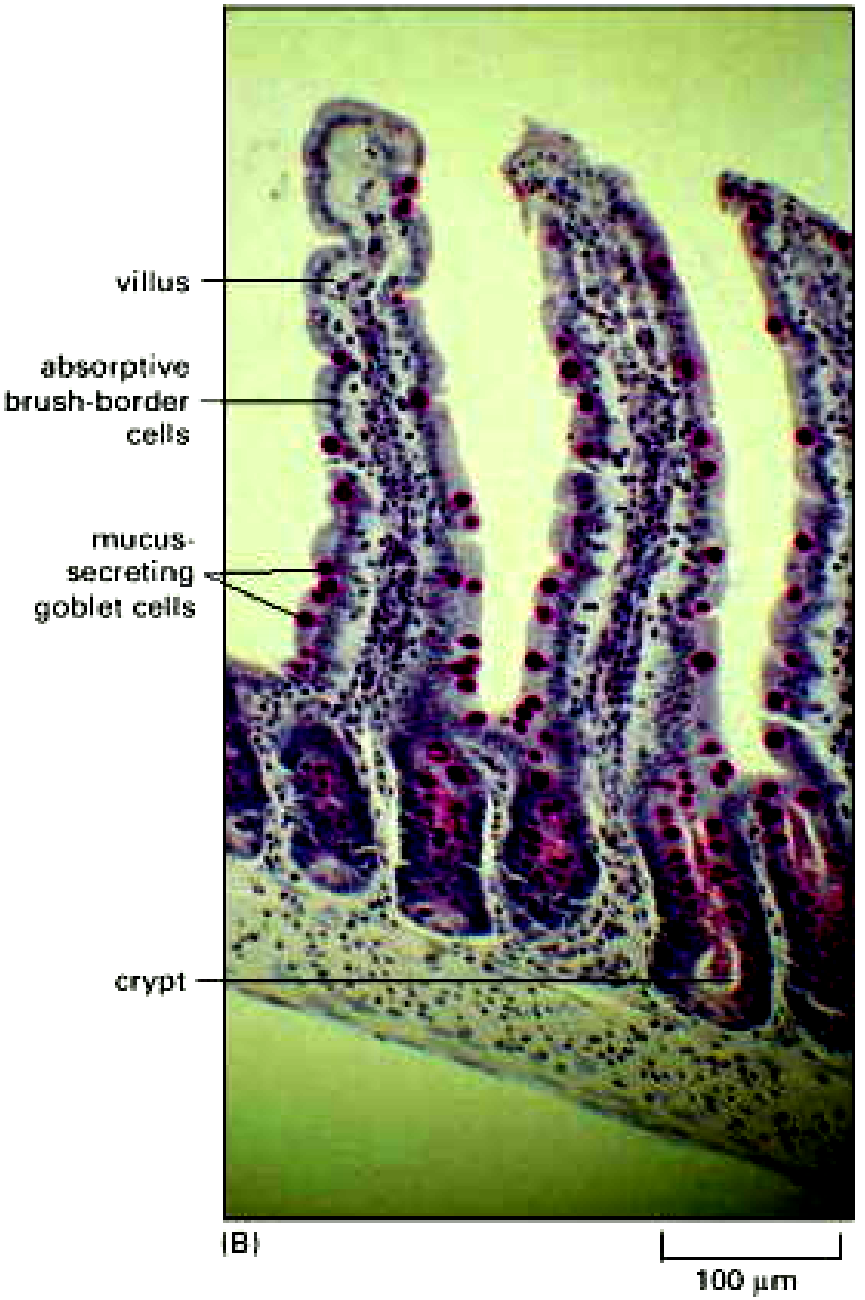

stem cell
committed
transit
amplifying cell
terminally
differentiated
cells

PIEL


squame about to flake off from surface
keratinized squames
granular cell layer
prickle cell layers
basal cell layer
basal lamina
connective tissue of dermis
EPIDERMIS
DERMIS
30 µm
basal cell passing into prickle cell layer
basal cell dividing

EPITELIO INTESTINAL



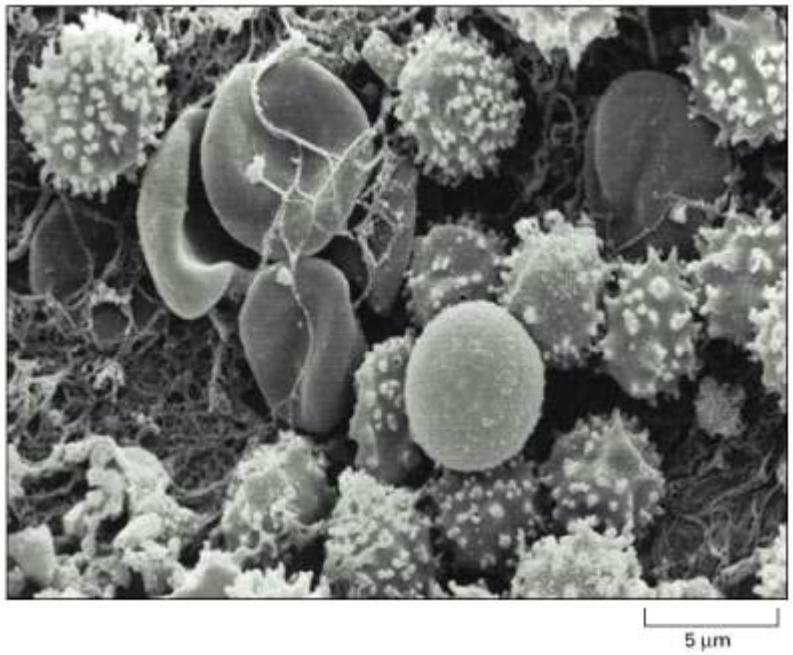


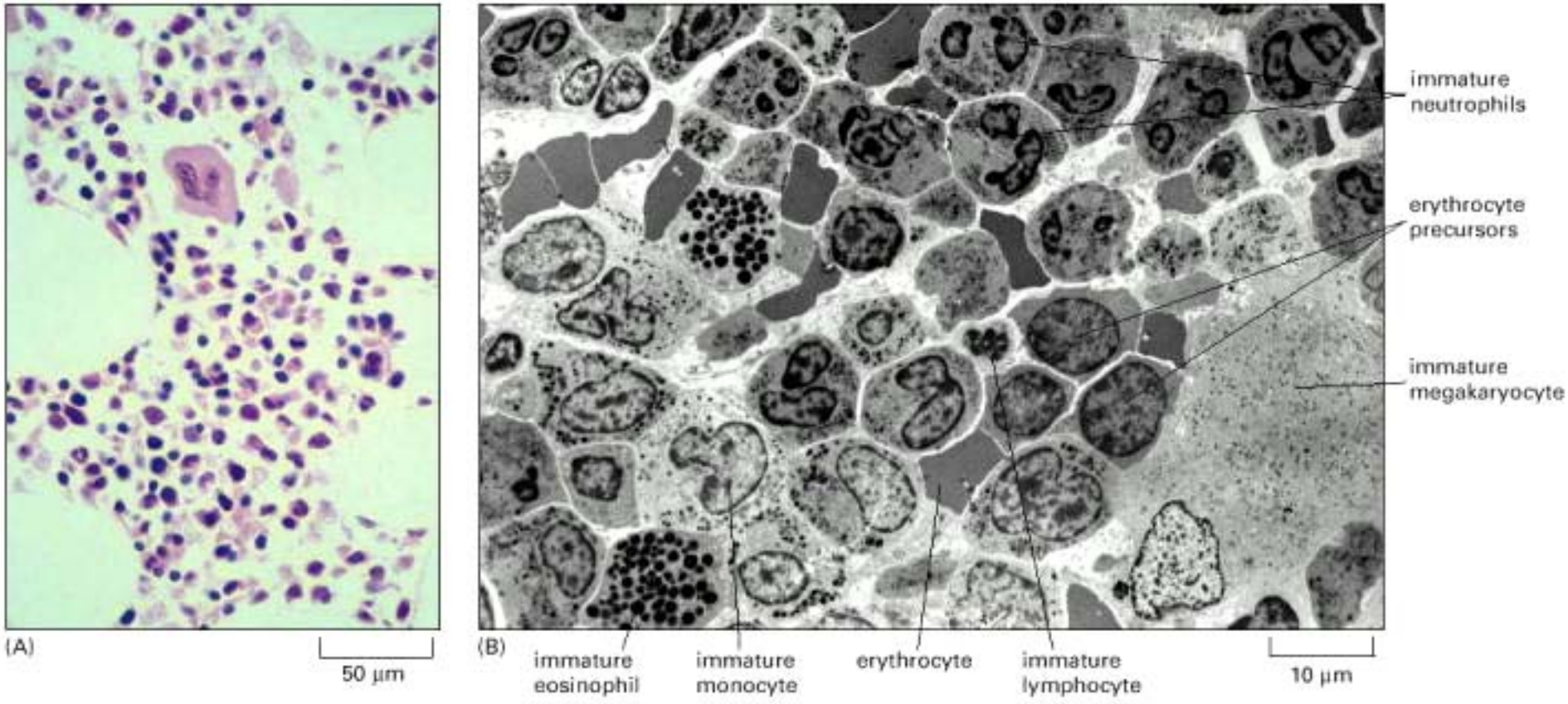
TEJIDOS EN RENOVACIÓN

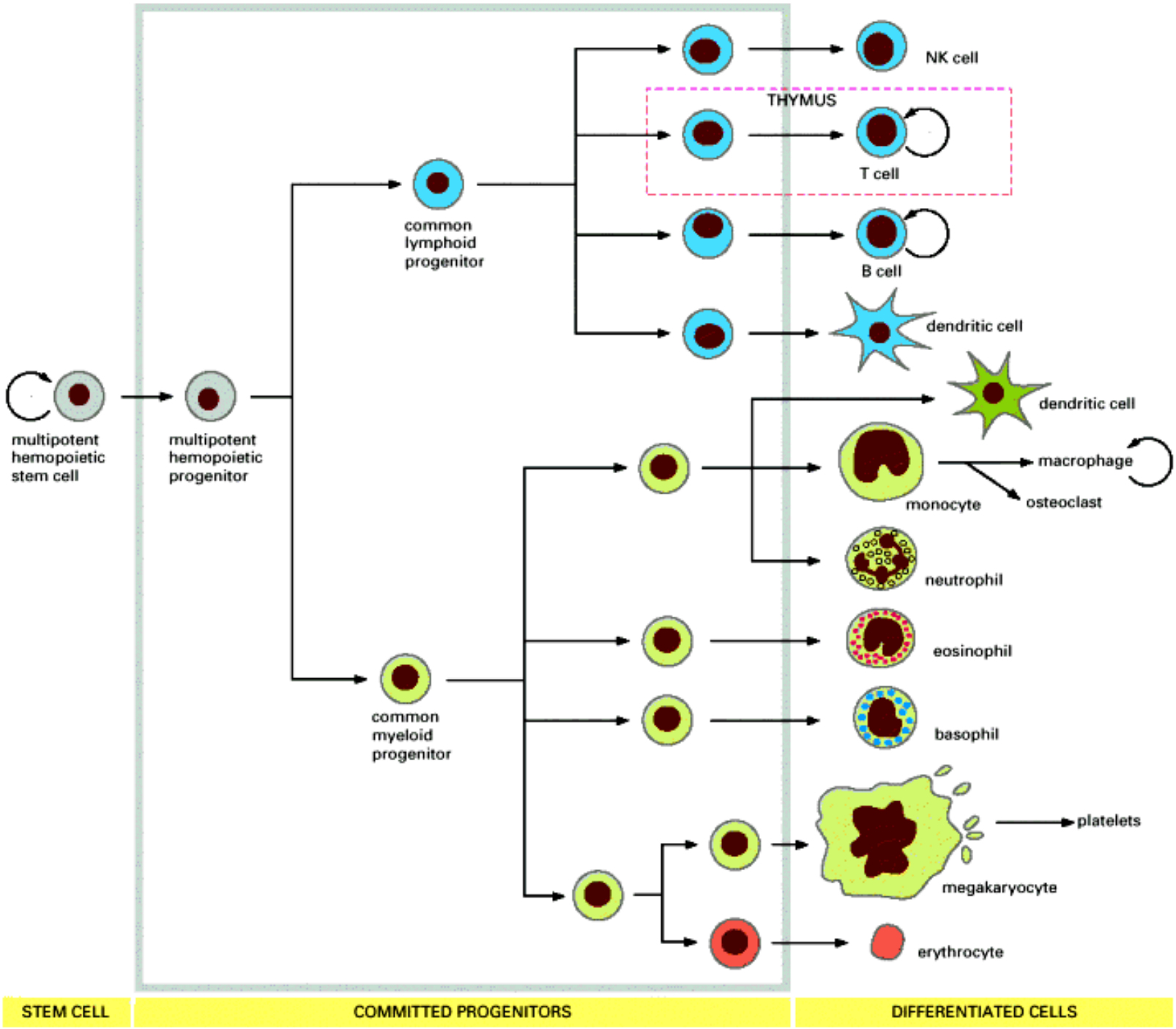
STEM CELL - CÉLULAS TRONCALES

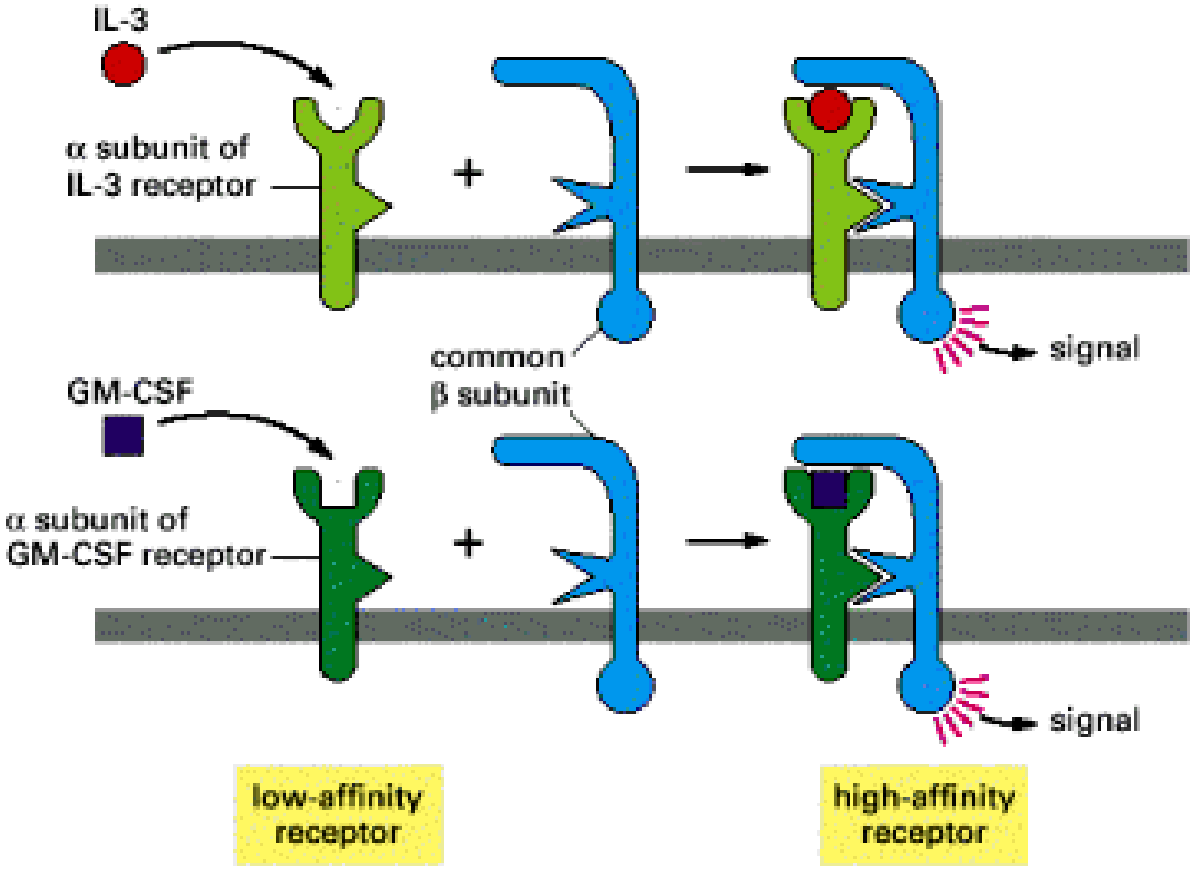
PLURIPOTENCIALES

CÉLULAS DE LA SANGRE



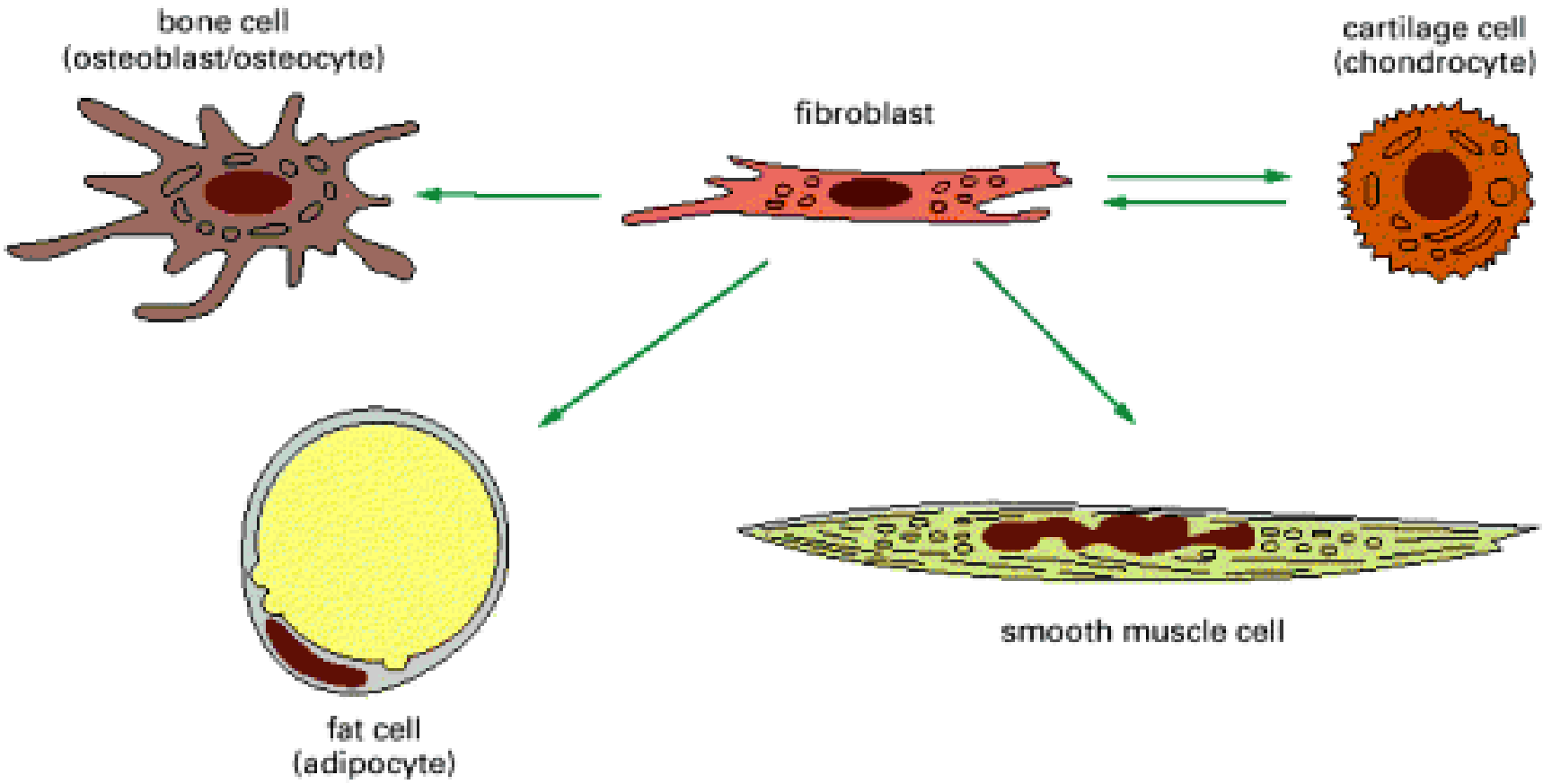

(A)
50 µm
(B)
immature neutrophils
erythrocyte precursors
immature megakaryocyte
immature eosinophil
immature monocyte
erythrocyte
immature lymphocyte
10 µm


multipotent hemopoietic stem cell
multipotent hemopoietic progenitor
common lymphoid progenitor
common myeloid progenitor
THYMUS
NK cell
T cell
B cell
dendritic cell
dendritic cell
monocyte
macrophage
osteoclast
neutrophil
eosinophil
basophil
megakaryocyte
platelets
erythrocyte
STEM CELL
COMMITTED PROGENITORS
DIFFERENTIATED CELLS

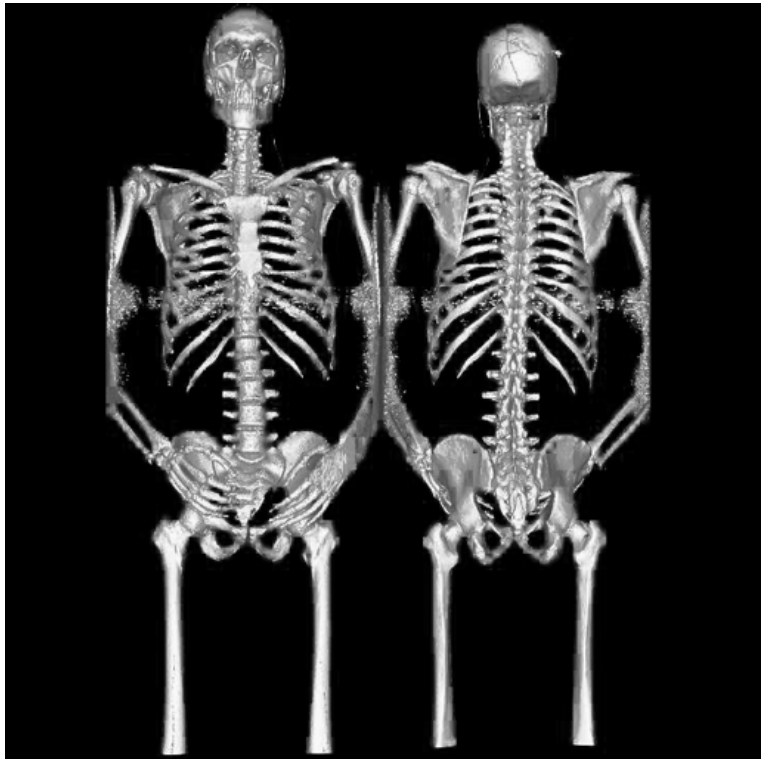

IL-3
α subunit of
IL-3 receptor
common
β subunit
signal
GM-CSF
α subunit of
GM-CSF receptor
signal
low-affinity
receptor
high-affinity
receptor

FACTOR	TARGET CELLS	PRODUCING CELLS	RECEPTORS
Erythropoietin	CFC-E	kidney cells	cytokine family
Interleukin 3 (IL-3)	multipotent stem cell, most progenitor cells, many terminally differentiated cells	T lymphocytes, epidermal cells	cytokine family
Granulocyte/ macrophage CSF (GM-CSF)	GM progenitor cells	T lymphocytes, endothelial cells, fibroblasts	cytokine family
Granulocyte CSF (G-CSF)	GM progenitor cells and neutrophils	macrophages, fibroblasts	cytokine family
Macrophage CSF (M-CSF)	GM progenitor cells and macrophages	fibroblasts, macrophages, endothelial cells	receptor tyrosine kinase family
Steel factor (stem cell factor)	hemopoietic stem cells	stromal cells in bone marrow and many other cells	receptor tyrosine kinase family

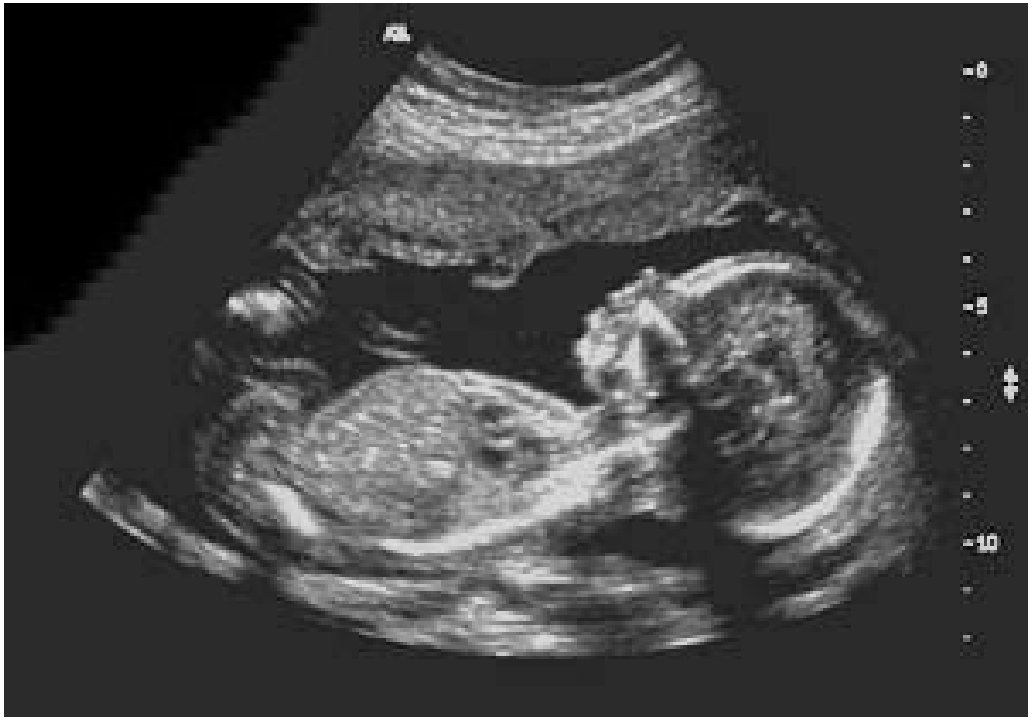
TEJIDO CONJUNTIVO – CÉLULAS MESENQUIMÁTICAS
FIBROBLASTOS INMADUROS

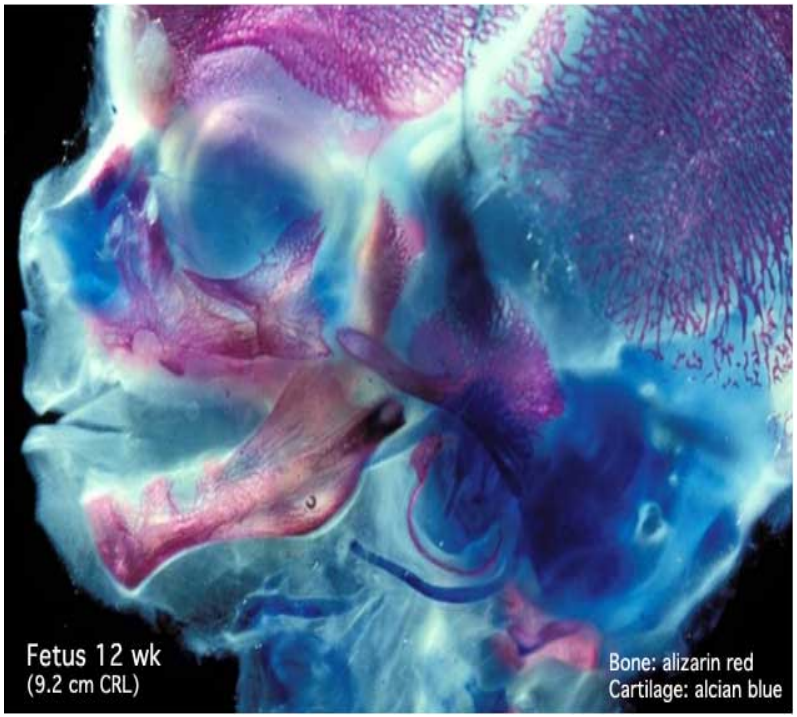

bone cell
(osteoblast/osteocyte)
fibroblast
cartilage cell
(chondrocyte)
fat cell
(adipocyte)
smooth muscle cell

EL SISTEMA OSEO COMO MODELO PARA COMPRENDER EL PROCESO DE DIFERENCIACIÓN CELULAR

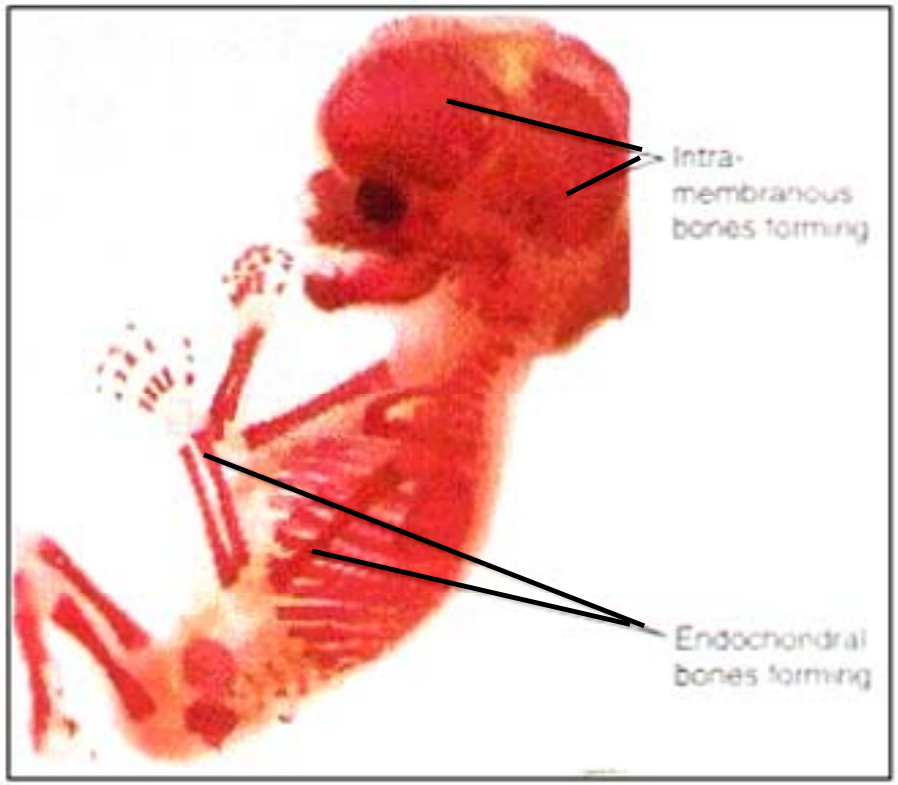


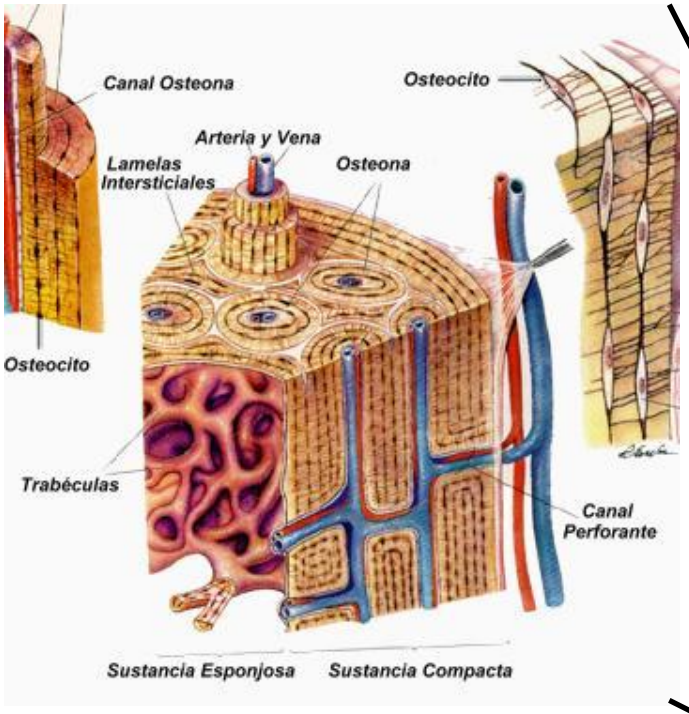
Formación Ósea

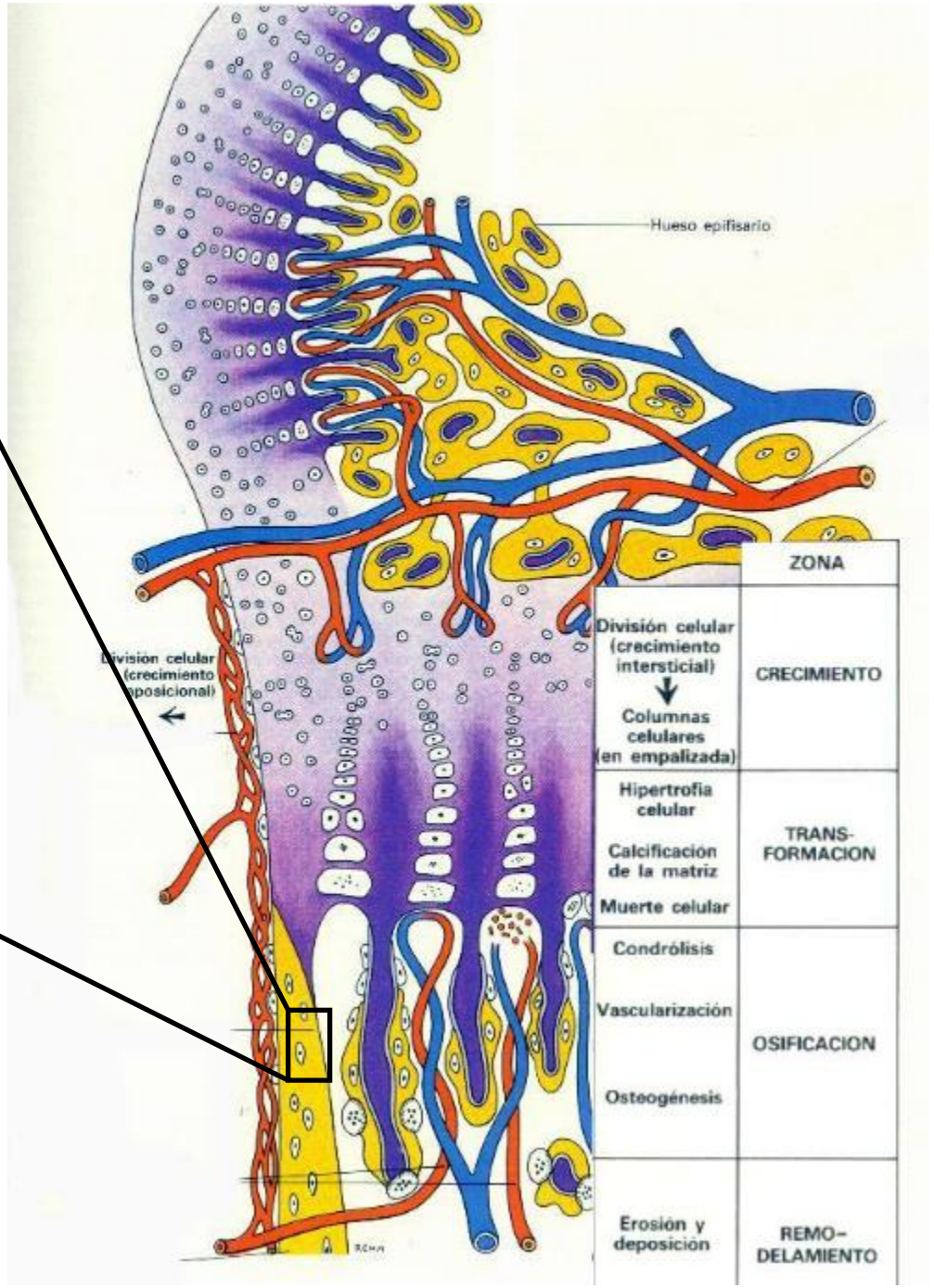


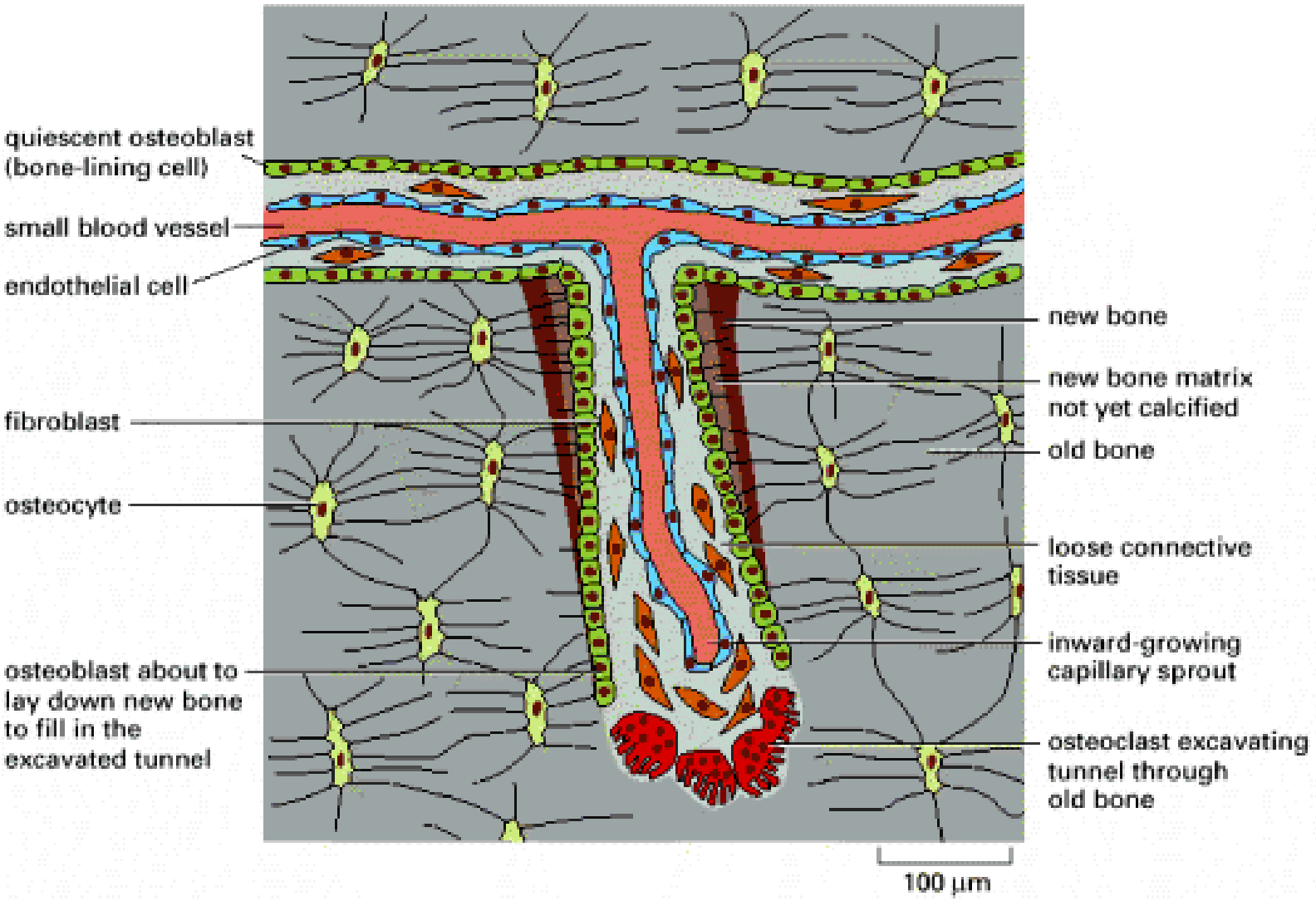


FORMACION OSEA

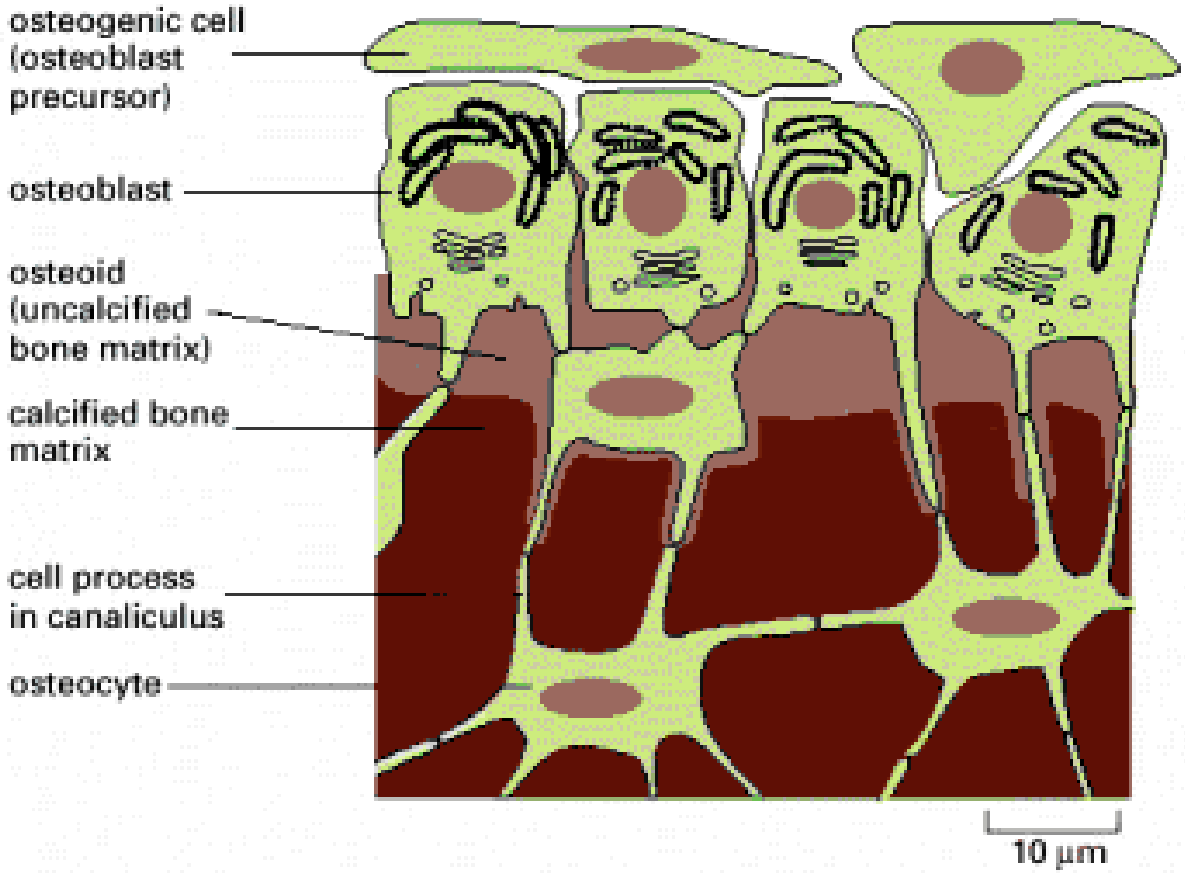



Canal Osteona
Osteocito
Arteria y Vena
Lamelas Intersticiales
Osteona
Osteocito
Trabéculas
Canal Perforante
Sustancia Esponjosa
Sustancia Compacta

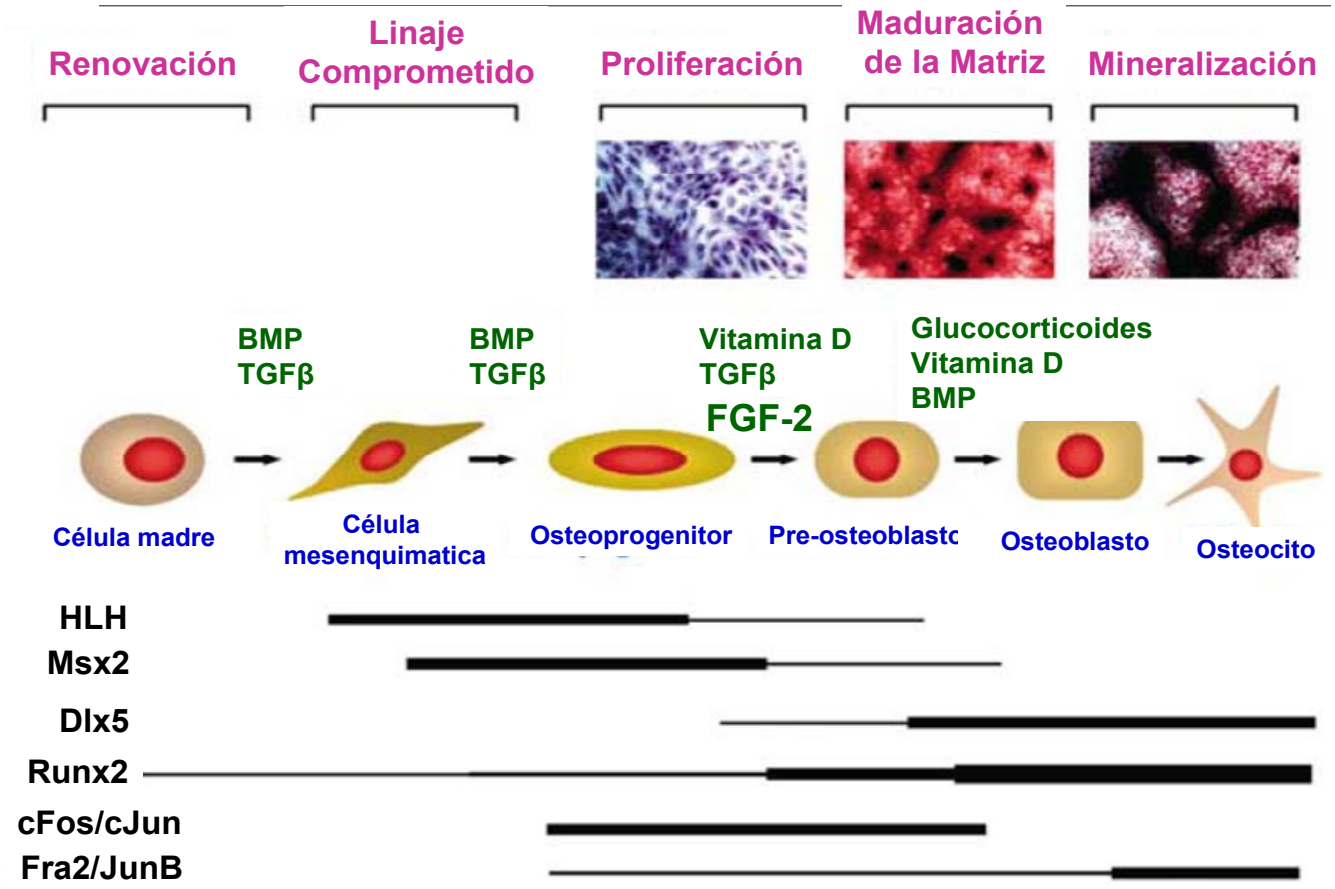

Hueso epifisario
División celular (crecimiento intersticial)
Columnas celulares (en empalizada)
Hipertrofia celular
Calcificación de la matriz
Muerte celular
Condrólisis
Vascularización
Osteogénesis
Erosión y deposición
ZONA
CRECIMIENTO
TRANS-FORMACION
OSIFICACION
REMO-DELAMIENTO


quiescent osteoblast
(bone-lining cell)
small blood vessel
endothelial cell
fibroblast
osteocyte
osteoblast about to
lay down new bone
to fill in the
excavated tunnel
new bone
new bone matrix
not yet calcified
old bone
loose connective
tissue
inward-growing
capillary sprout
osteoclast excavating
tunnel through
old bone
100 μm

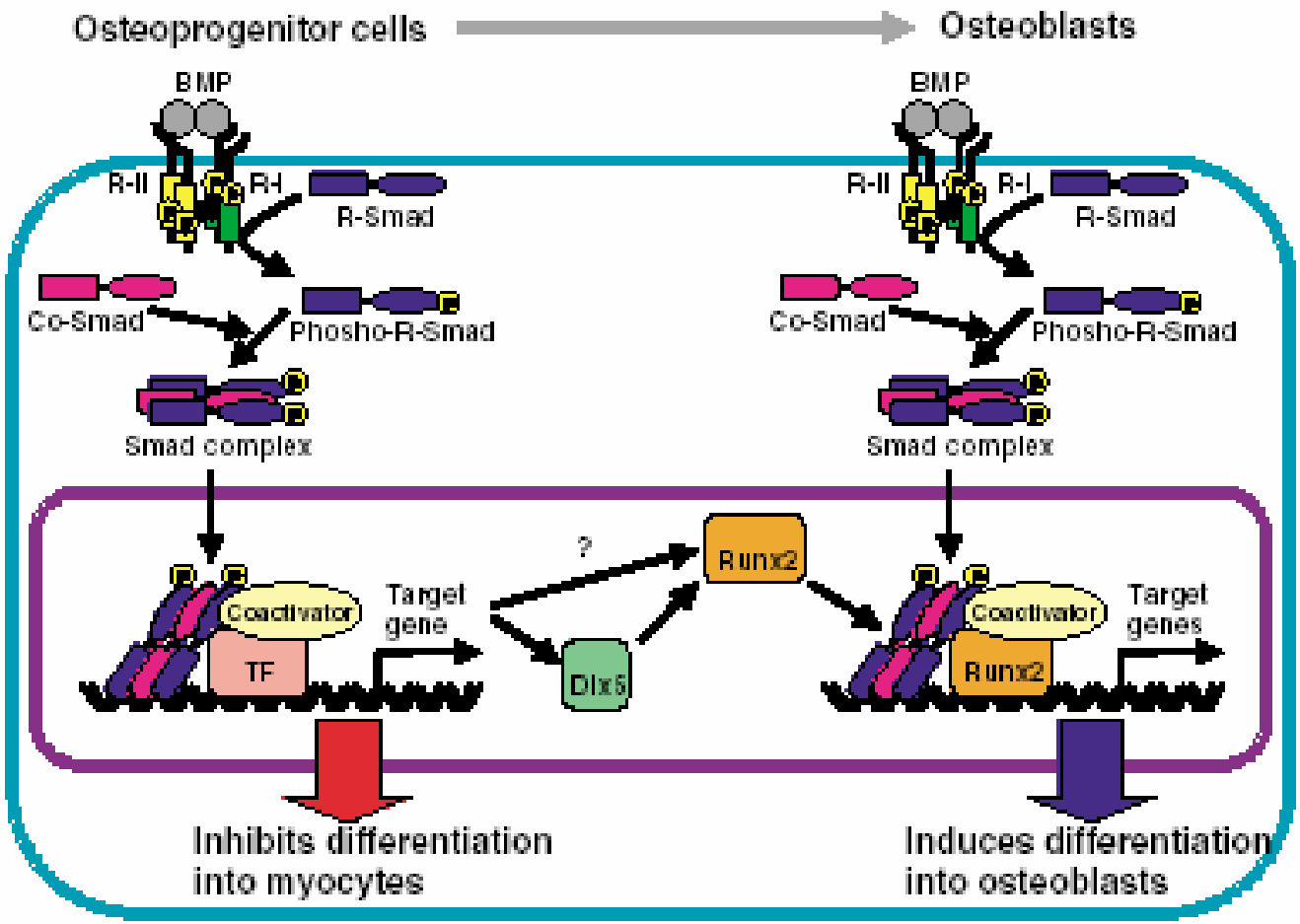
OSTEOBLASTOS



PROLIFERACION Y DIFERENCIACION DEL LINAJE CELULAR OSTEOBLASTICO

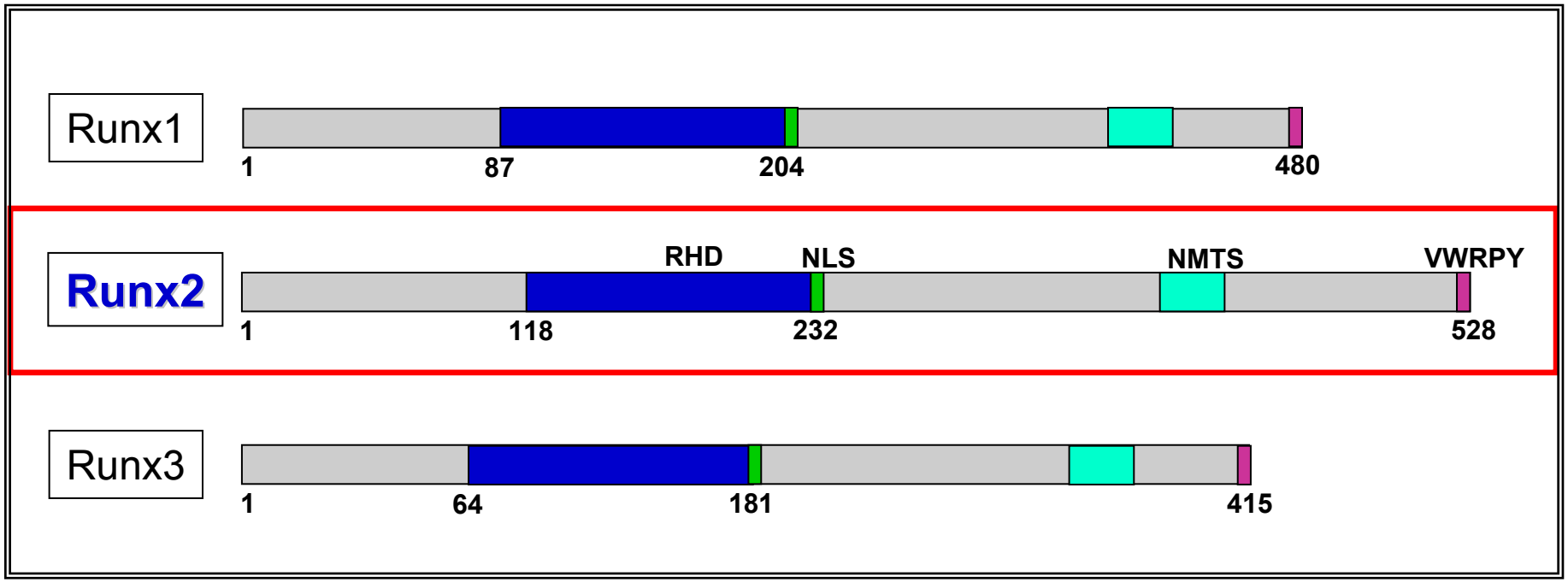


Stein y col., 2004


Osteoprogenitor cells
Osteoblasts
BMP
R-II
R-I
R-Smad
Co-Smad
Phosho-R-Smad
Smad complex
BMP
R-II
R-I
R-Smad
Co-Smad
Phosho-R-Smad
Smad complex
?
Runx2
Coactivator
TF
Target gene
Dlx5
Coactivator
Runx2
Target genes
Inhibits differentiation into myocytes
Induces differentiation into osteoblasts

EL FACTOR DE TRANSCRIPCIÓN RUNX2

DOMINIOS FUNCIONALES DE LAS PROTEINAS RUNX



RHD — ***Runt Homology Domain*** ***(DNA binding, Protein-Protein interaction)***

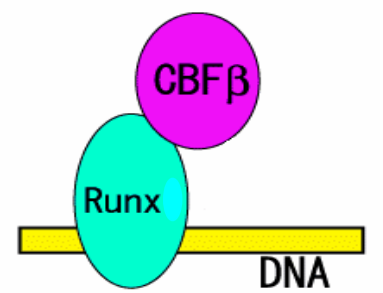
NSL — ***Nuclear Signaling Localization***

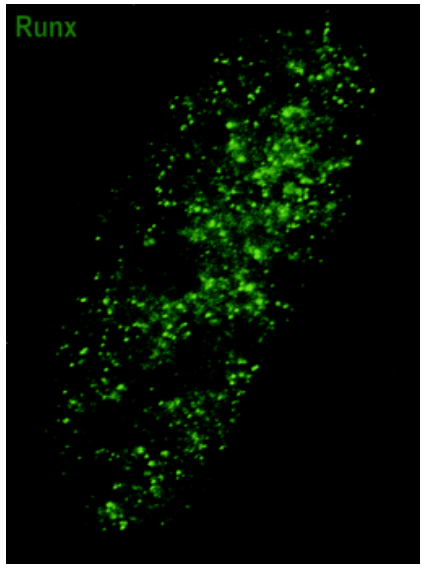
NMTS — ***Nuclear Matriz Targeting Signal*** ***(PST-Rich Domain)***

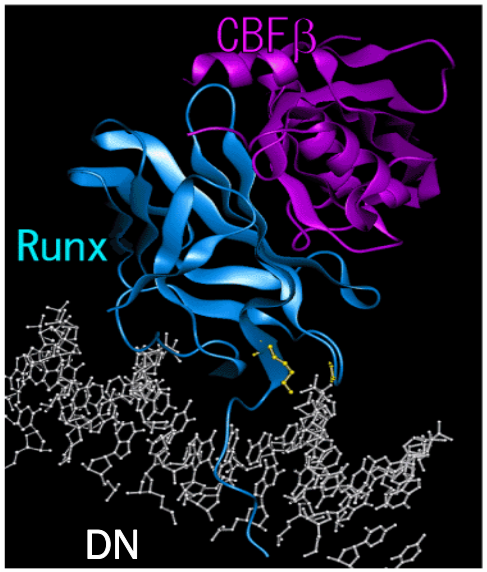
VWRPY — **Secuencia conservada de aminoácidos** ***(Groucho/TLE)***

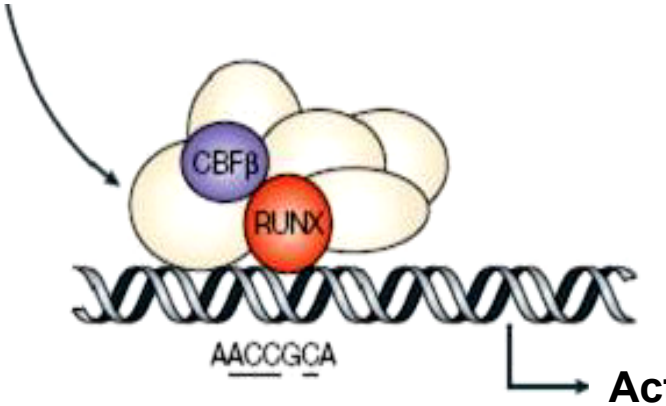
RUNX2
FACTOR DE TRANSCRIPCION

RUNX2 SE LOCALIZA EN EL NUCLEO DE LA CÉLULA

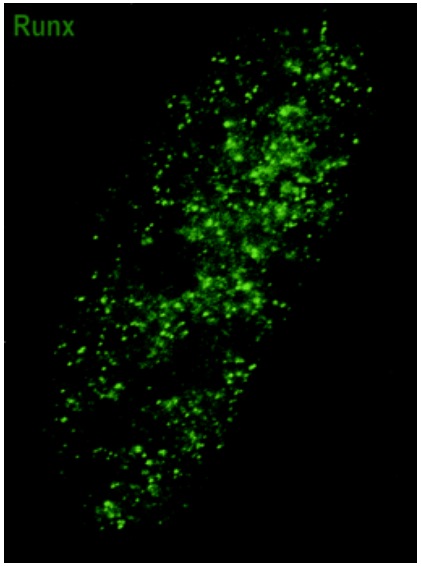








Activación de genes



a

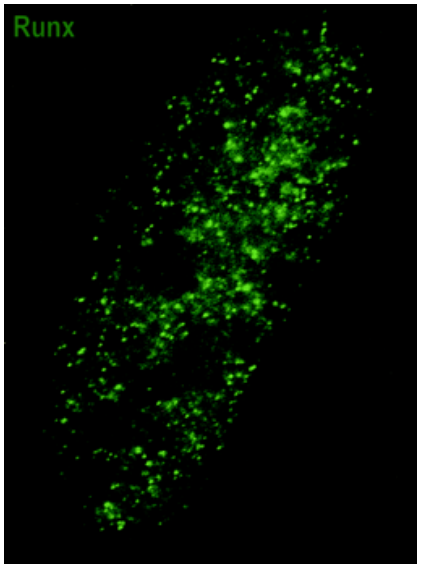
Inactive Osteocalcin Gene

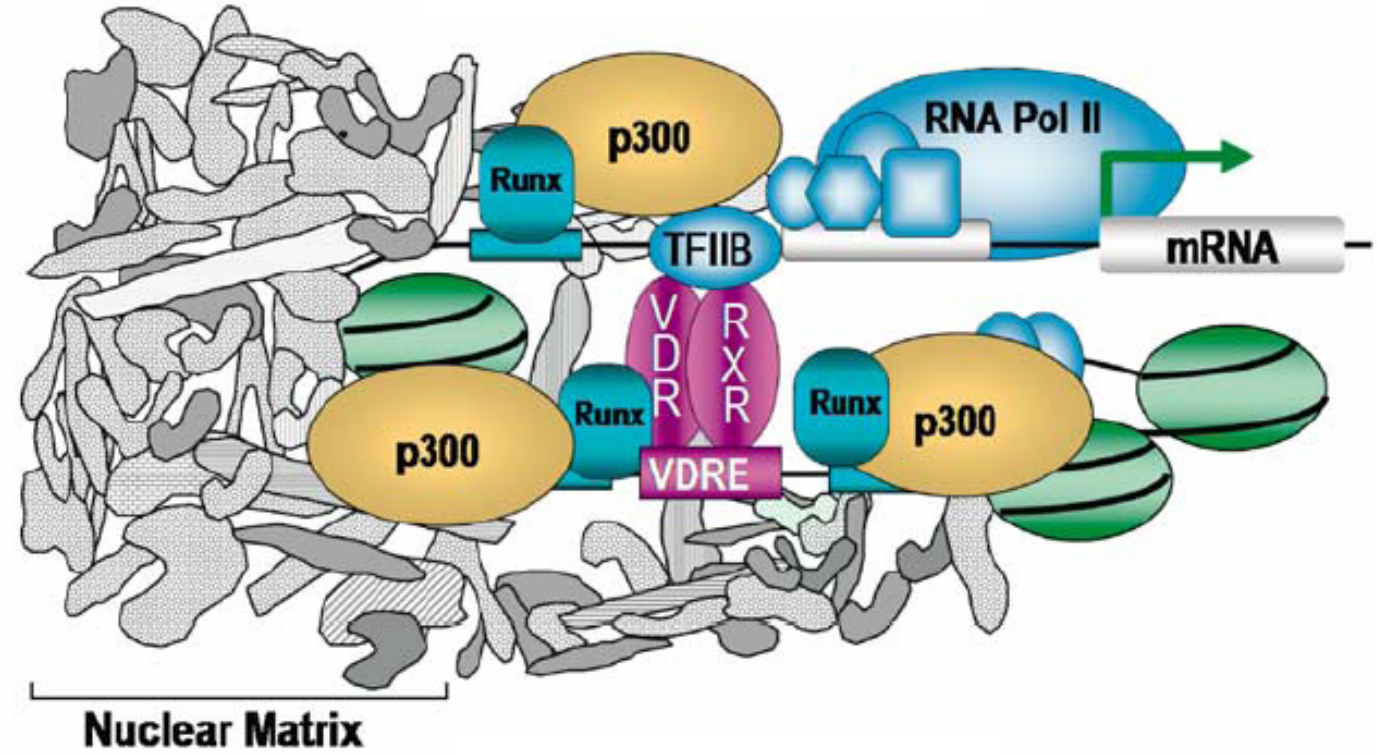
b

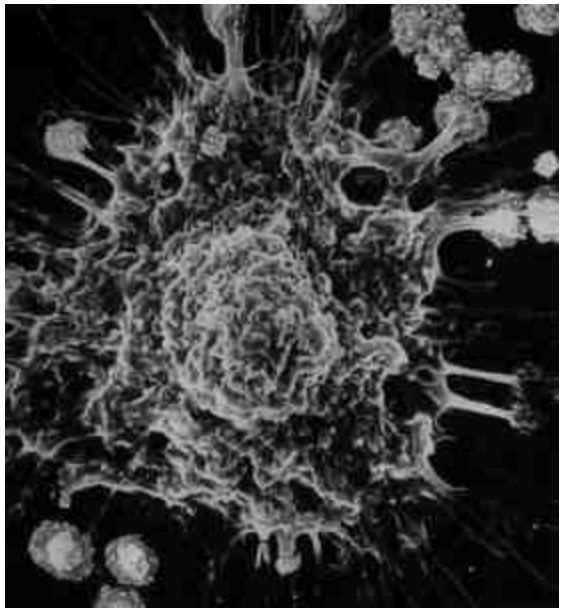
Basal Transcription of OC Gene

c

Vitamin D Induced Transcription of OC Gene

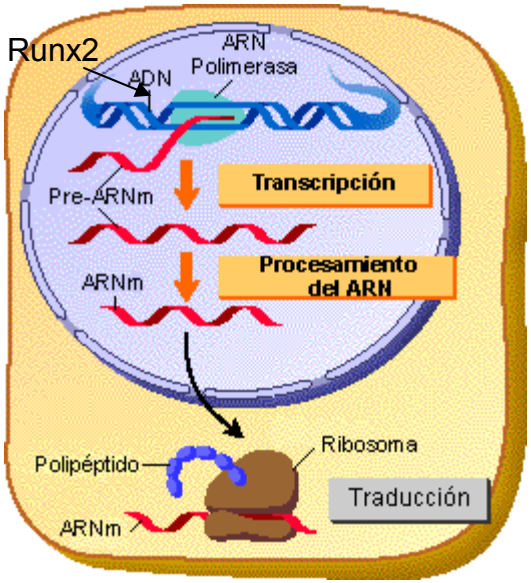

Runx

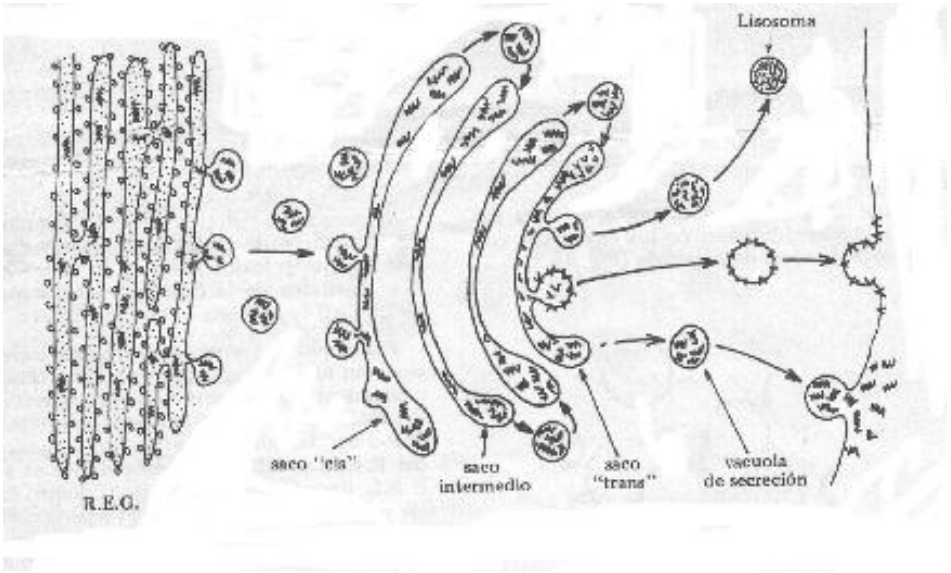

p300
Runx
RNA Pol II
TFIIB
mRNA
VDR
RXR
Runx
p300
Runx
p300
VDRE
Nuclear Matrix



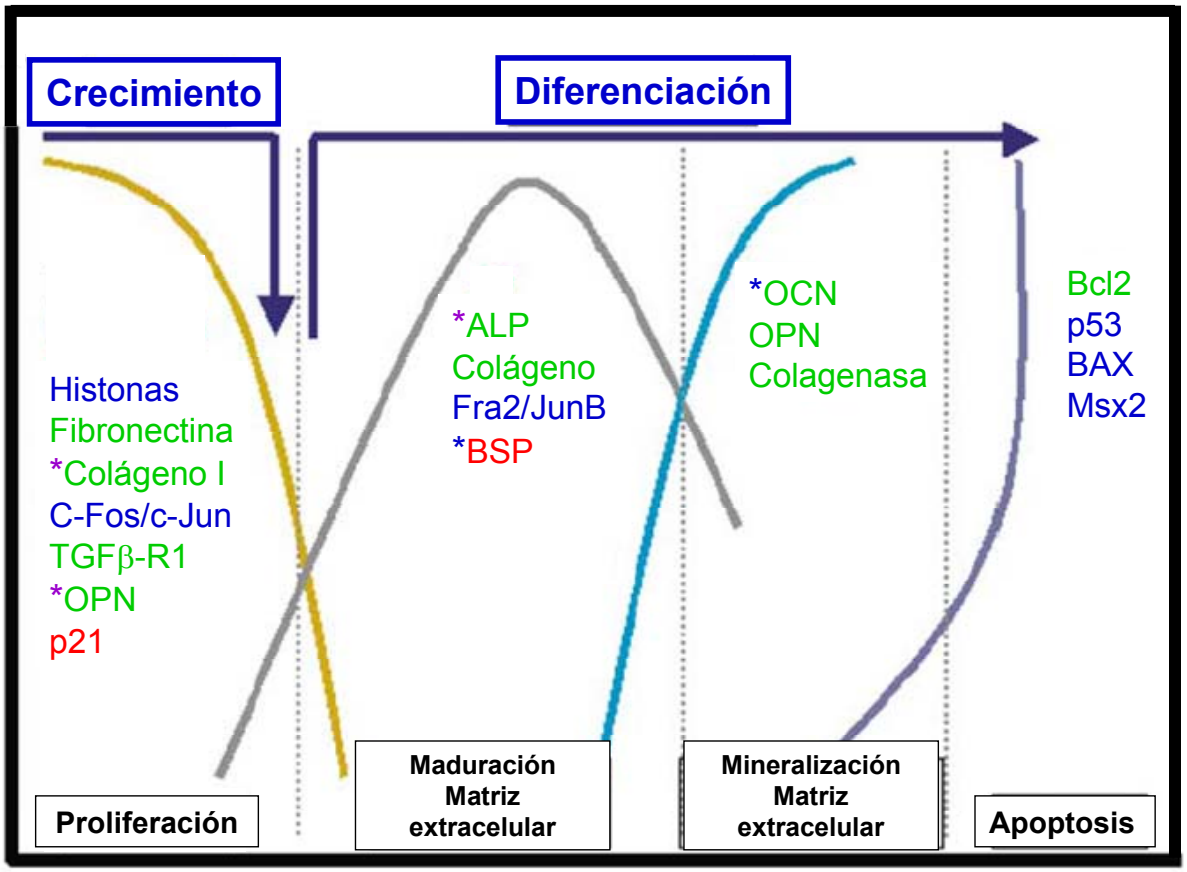
Osteoblasto

Osteoblasto es una célula especializada en la secreción de proteína que estructuran una matriz extracelular mineralizada.

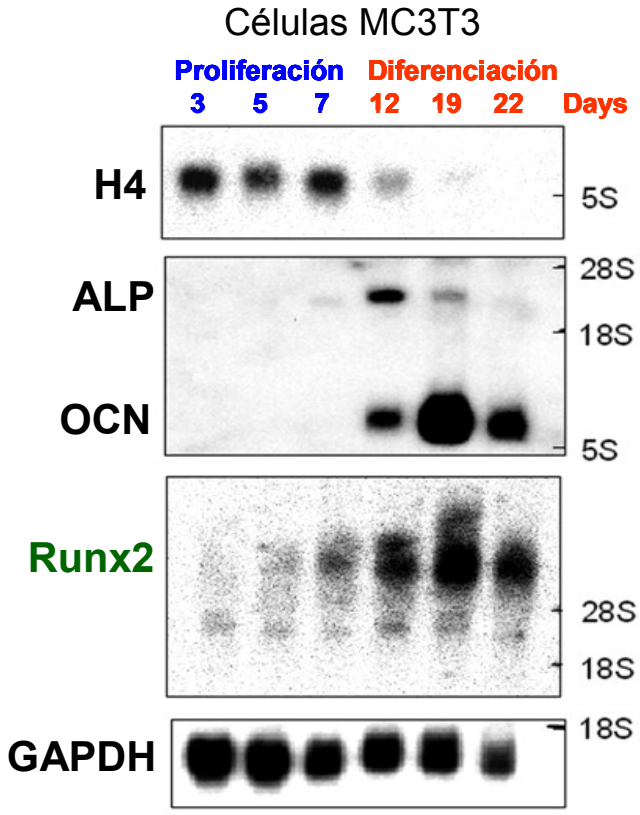




PROGRAMA DE EXPRESION GENICA ASOCIADA A PROLIFERACION Y DIFERENCIACION OSTEOBLASTICA



(En verde genes regulados positivamente por Runx2)



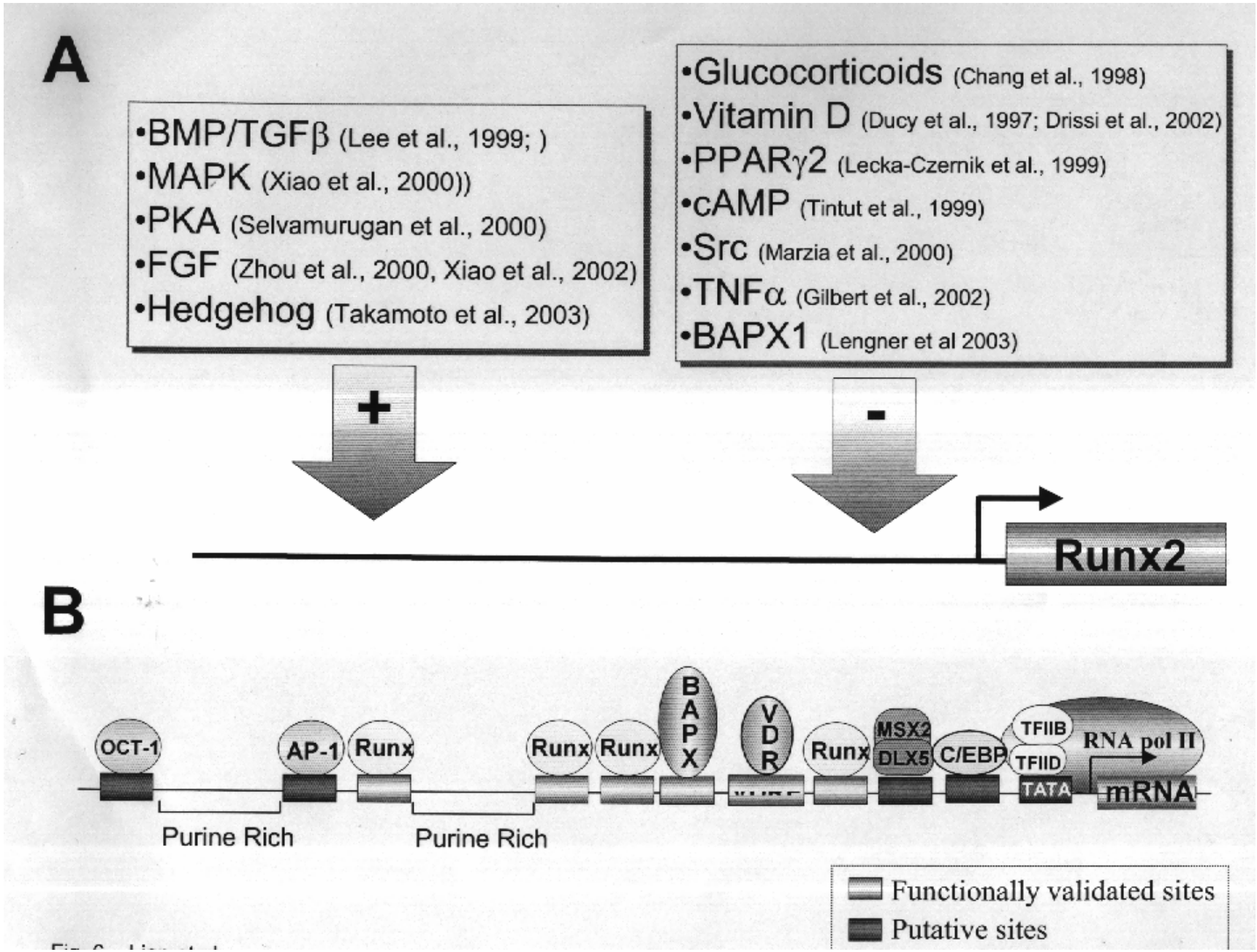
Niveles relativos de proteína Runx2

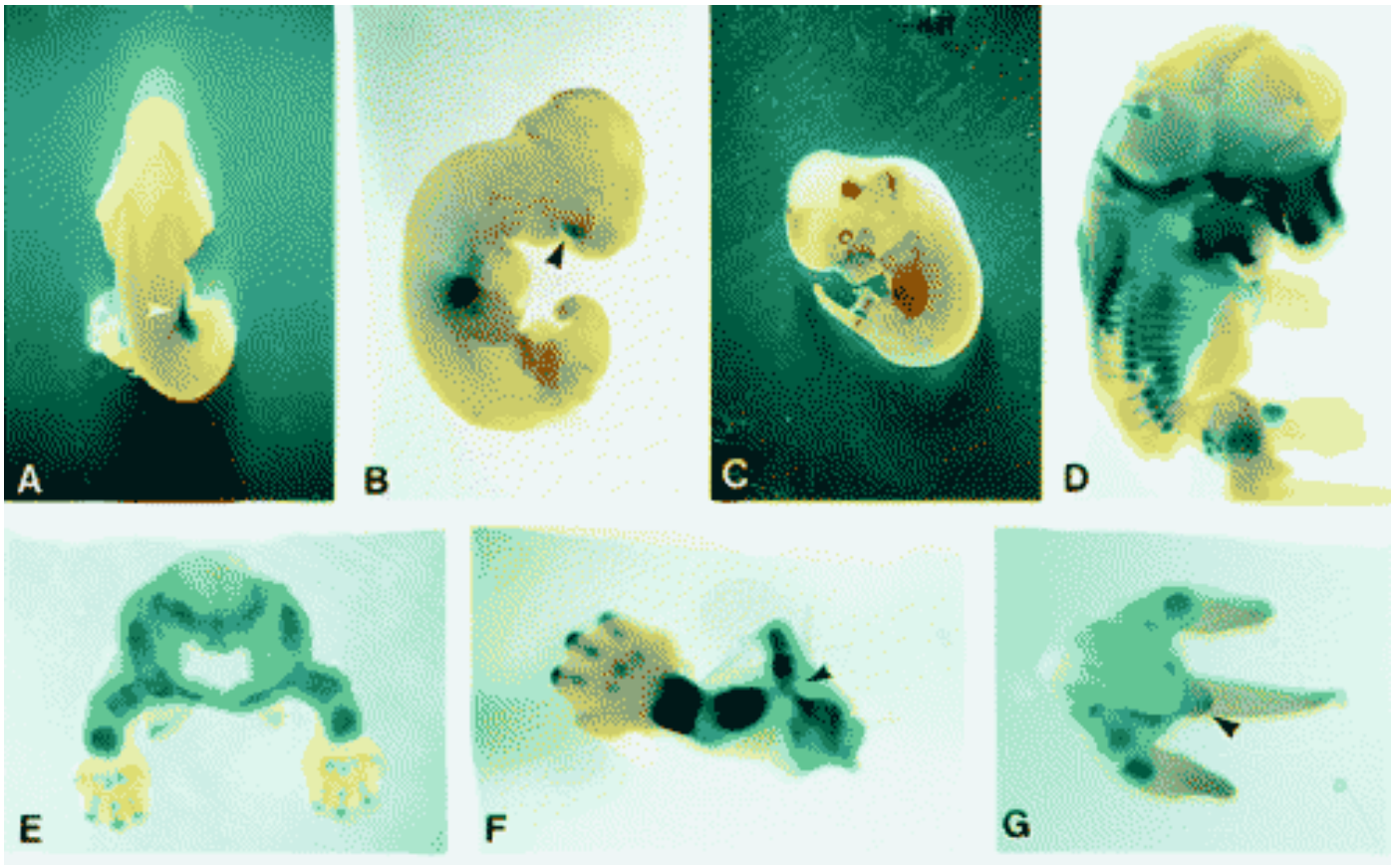
Stein y col., 2004

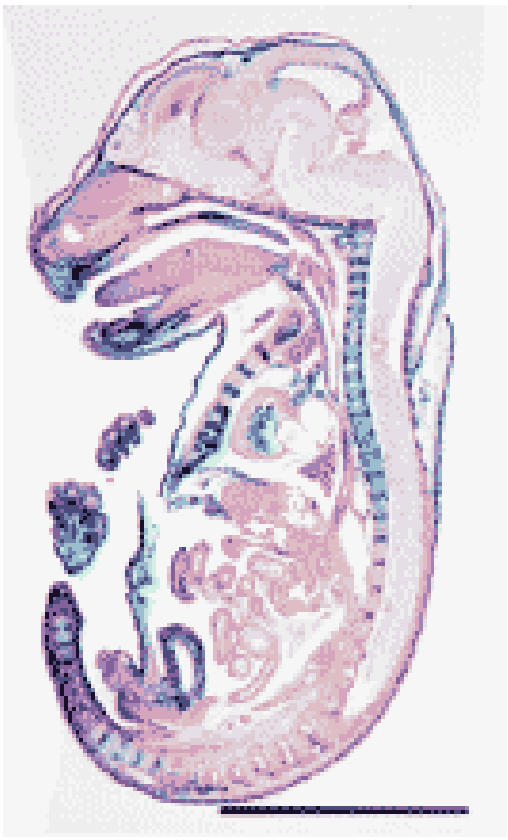
GENES REGULADOS POR RUNX2

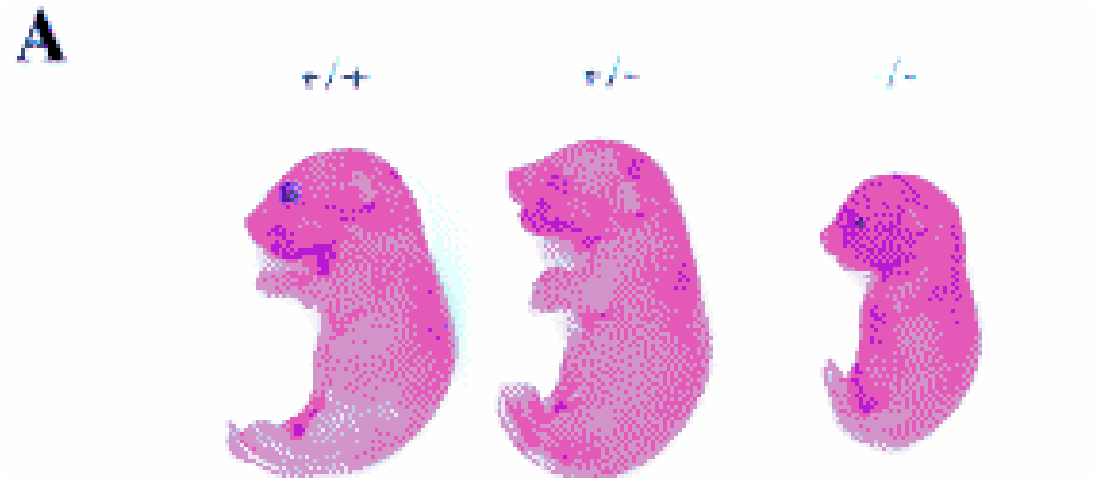
Bone Related	
- Runx2	[Drissi et al., 2000b]
- Collagen	[Enomoto et al., 2000], [Kern et al., 2001]
- TGFβ Receptor	[Ji et al., 1998]
- Estrogen Receptorα	[McCarthy et al., 2003; Sasaki-Iwaoka et al., 1999; Tou et al., 2001]
- Vitamin D receptor	[Sasaki-Iwaoka et al., 1999]
- Alkaline phosphatase	[Harada et al., 1999]
- Collagenase	[Hess et al., 2001; Jimenez et al., 1999; Selvamurugan et al., 1998; Selvamurugan et al., 2000]
- Type X collagen	[Zheng et al., 2003]
- Bone sialo protein	[Javed et al., 1999]
- Dentin sialo protein	[Chen et al., 2002b]
- Osteoprotegerin (RANKL)	[Thirunavukkarasu et al., 2000]
- Osteopontin	[Sato et al., 1998]
- Osteocalcin	[Ducy et al., 1997; Merriman et al., 1995]
- Galectin-3	[Stock et al., 2003]
- C/EBPδ	[McCarthy et al., 2000]

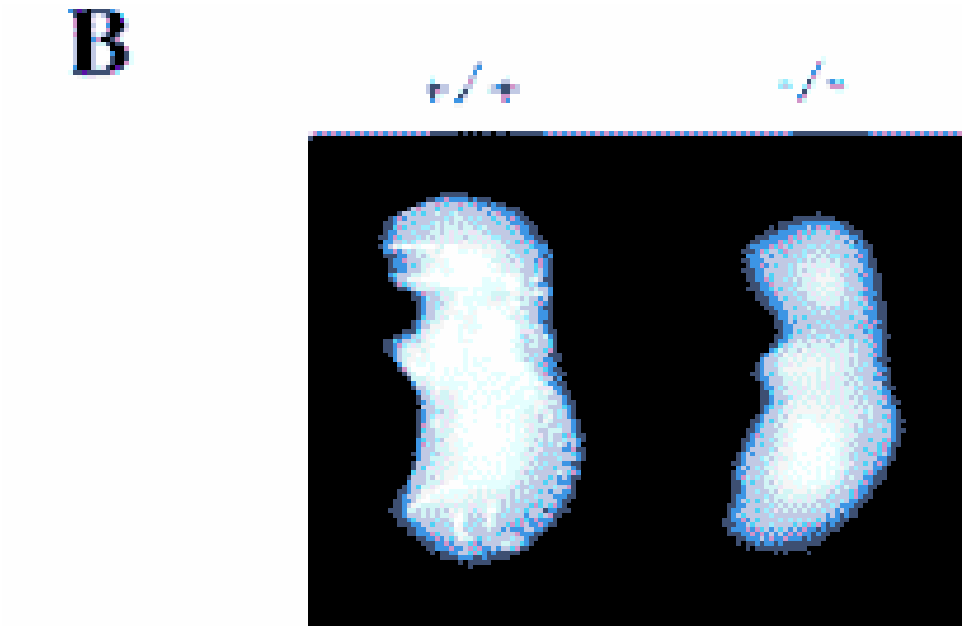
SENALES EXTRACELULARES ACTIVAN LA TRANSCRIPCIÓN DEL GEN RUNX2

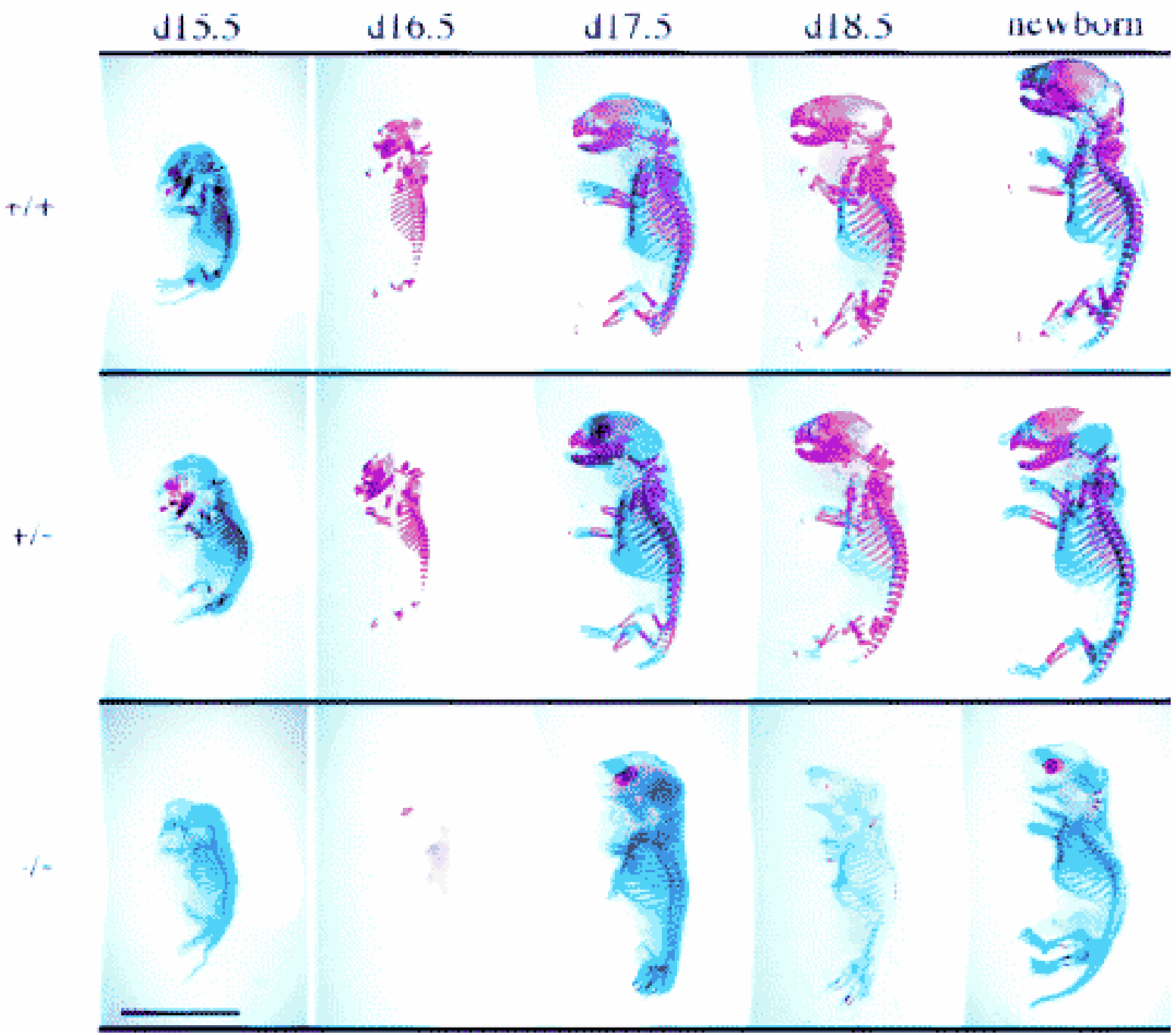


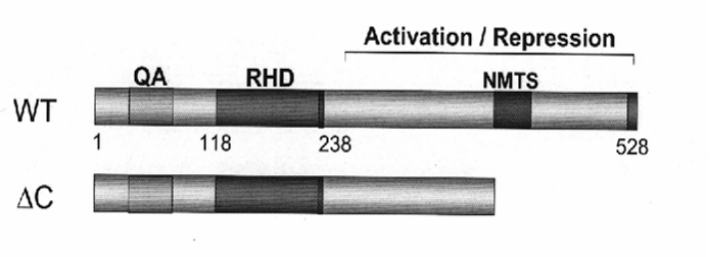

A
B
C
D
E
F
G

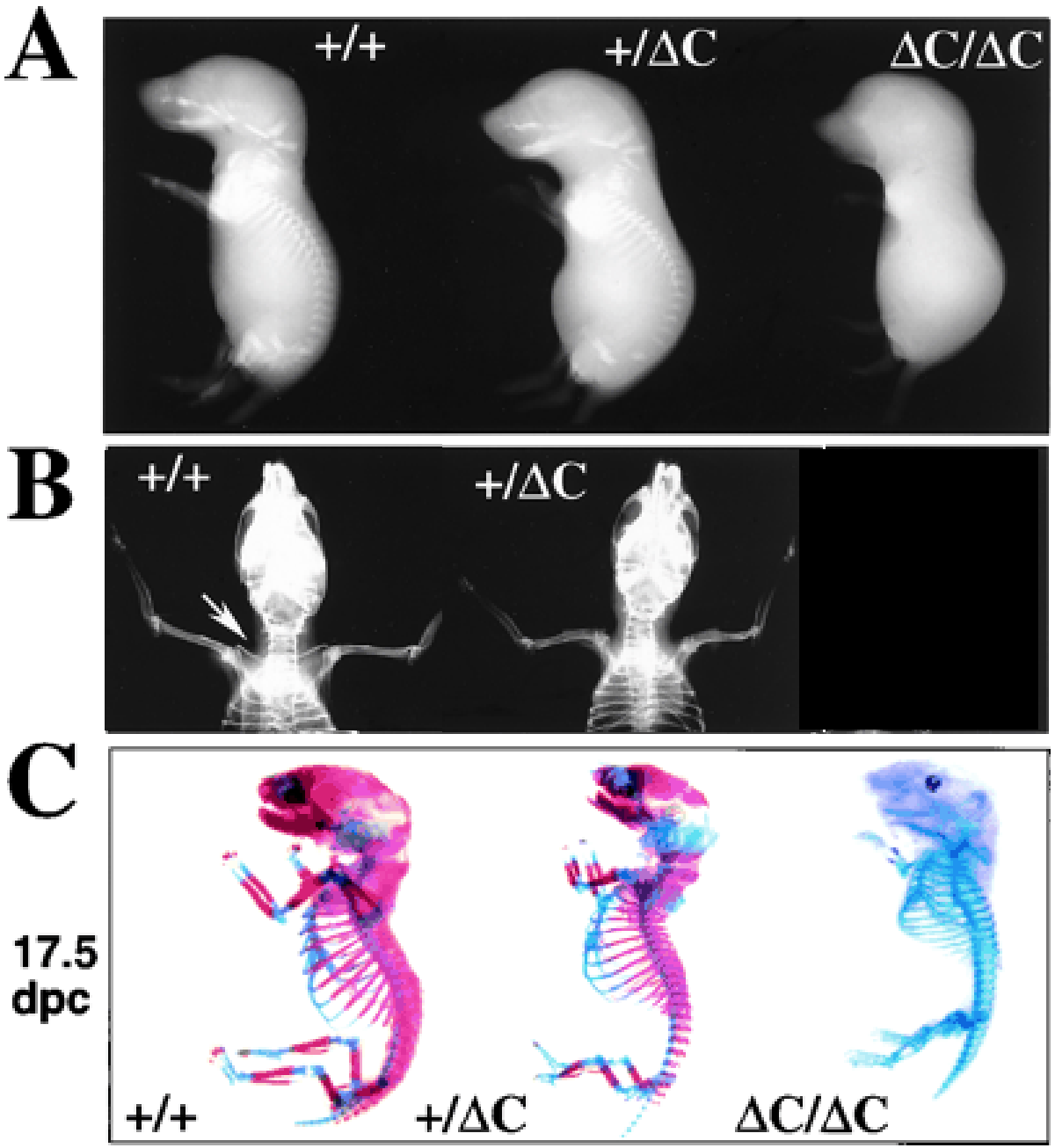



A
+/+
+/-
-/-

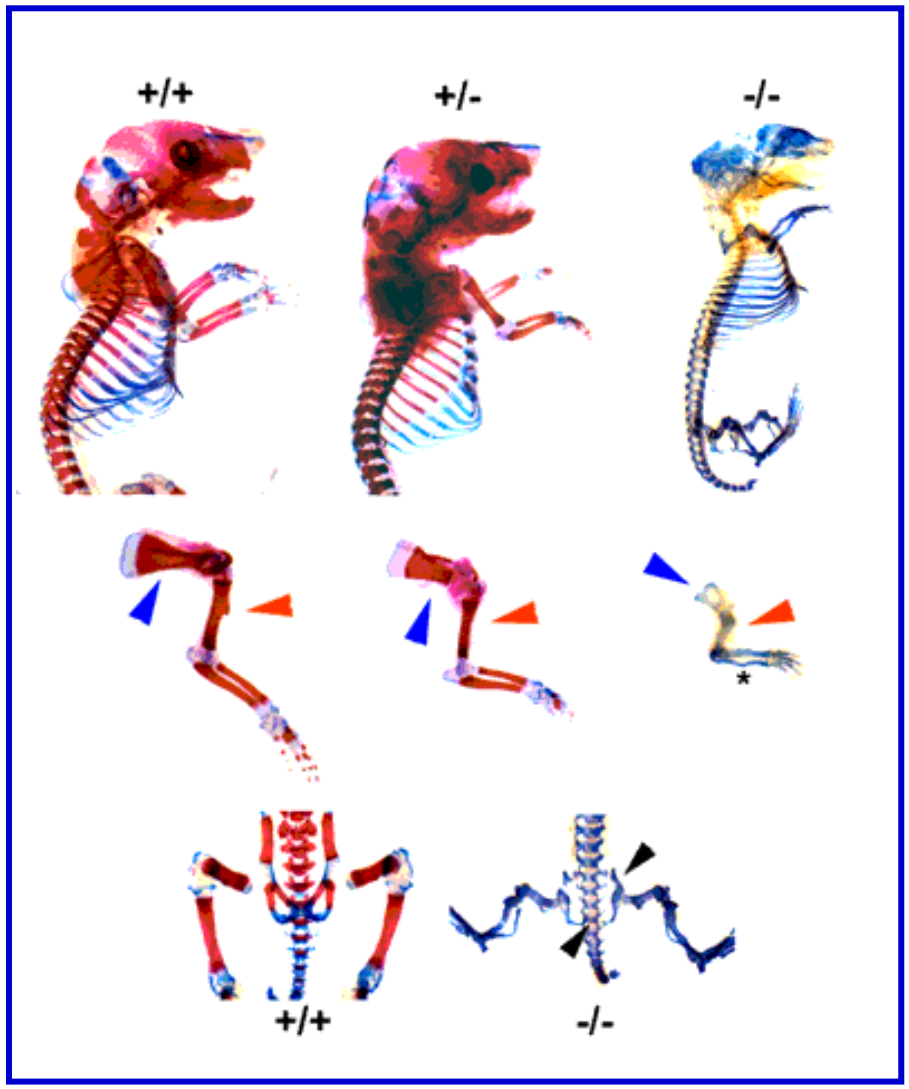

B
+/+
-/-


d15.5
d16.5
d17.5
d18.5
newborn
+/+
+/-
-/-


Activation / Repression
QA
RHD
NMTS
WT
1
118
238
528
ΔC


A
+/+
+/ΔC
ΔC/ΔC
B
+/+
+/ΔC
C
17.5
dpc
+/+
+/ΔC
ΔC/ΔC

IMPORTANCIA DE RUNX2 EN LA DIFERENCIACION OSEA



Fenotipo esqueletal en ratones

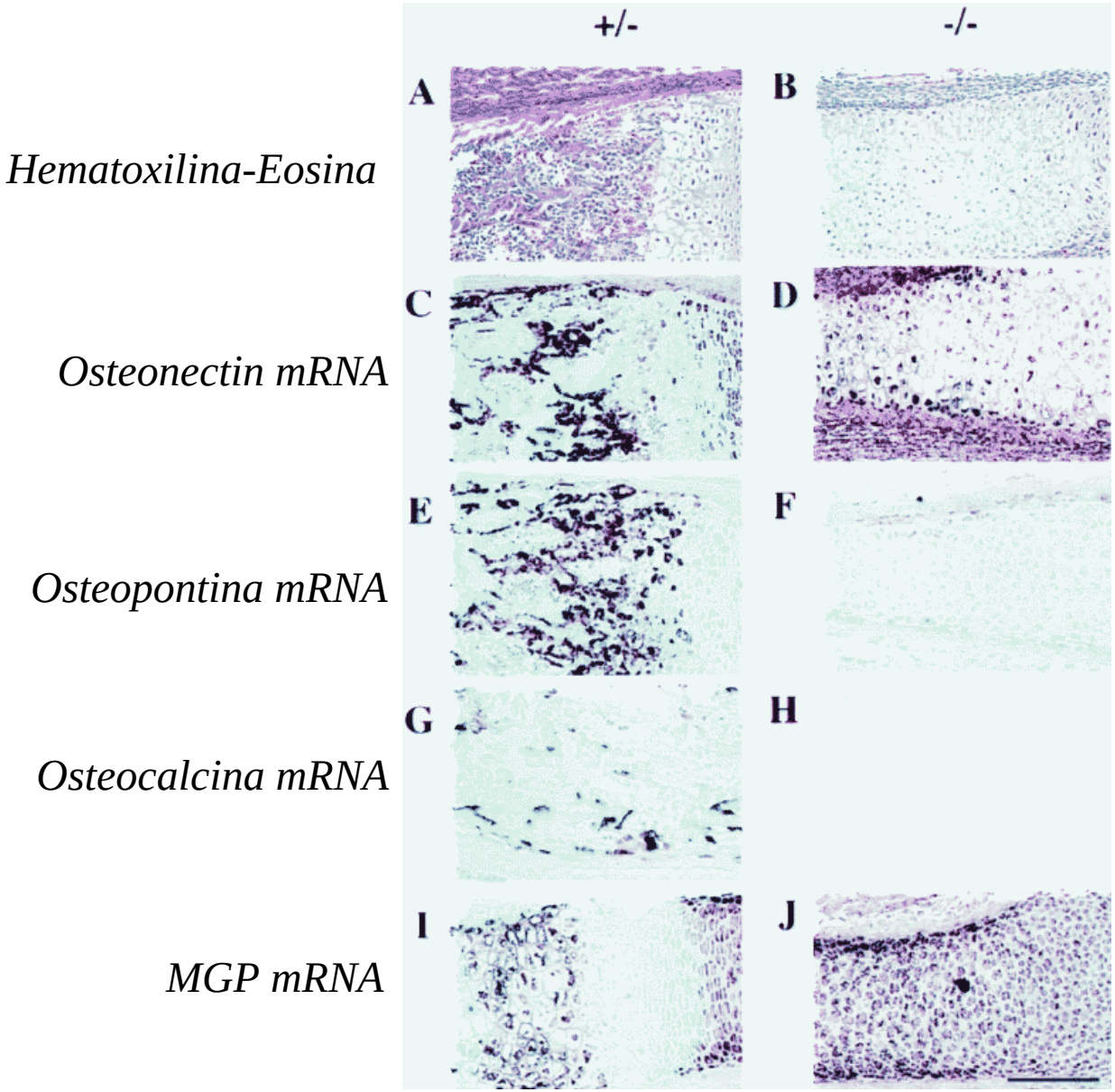
- wt (Runx2 +/+)

- heterocigoto (Runx2 +/-)

- homocigoto (Runx2 -/-) *knock out*

Nótese la ausencia completa de tinción roja (hueso) en el ratón Runx -/- .

Komori y cols., 1987.



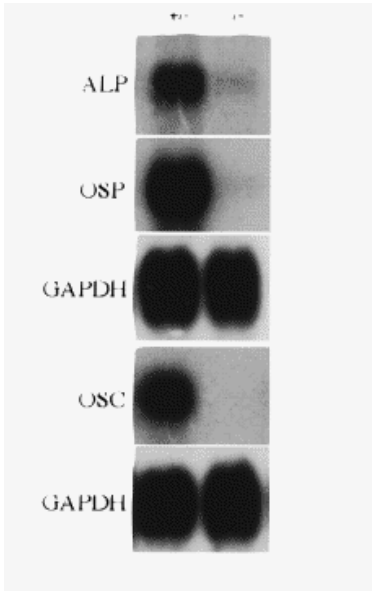
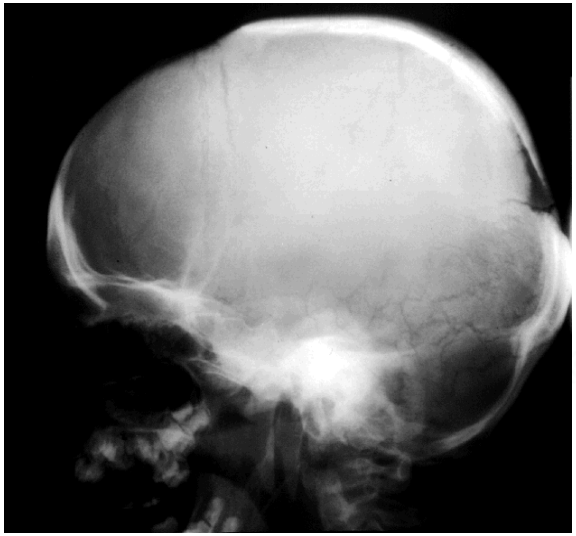
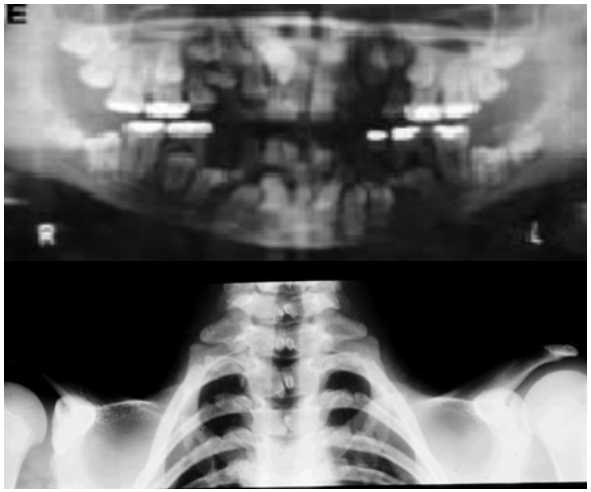


Figure 5. Distribution of *Osteonectin*, *Osteopontin*, *Osteocalcin*, and *MGP* mRNA(A, C, E, G, and I) Radius from d18.5 control (+/−) embryo. (B, D, F, H, and J) Radius from d18.5 mutant (−/−) embryo. (A and B) Staining with hematoxylin and eosin. (C and D) In situ hybridization by *Osteonectin* antisense probe. (E and F) *Osteopontin* antisense probe. (G and H) *Osteocalcin* antisense probe. (I and J) *MGP* antisense probe. Bar = 0.15 mm.

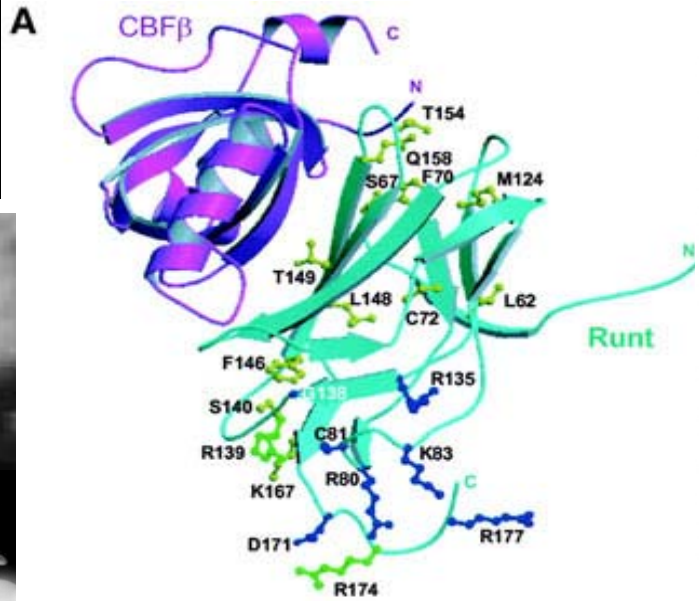
Rol de Runx2 en el proceso de diferenciación ósea

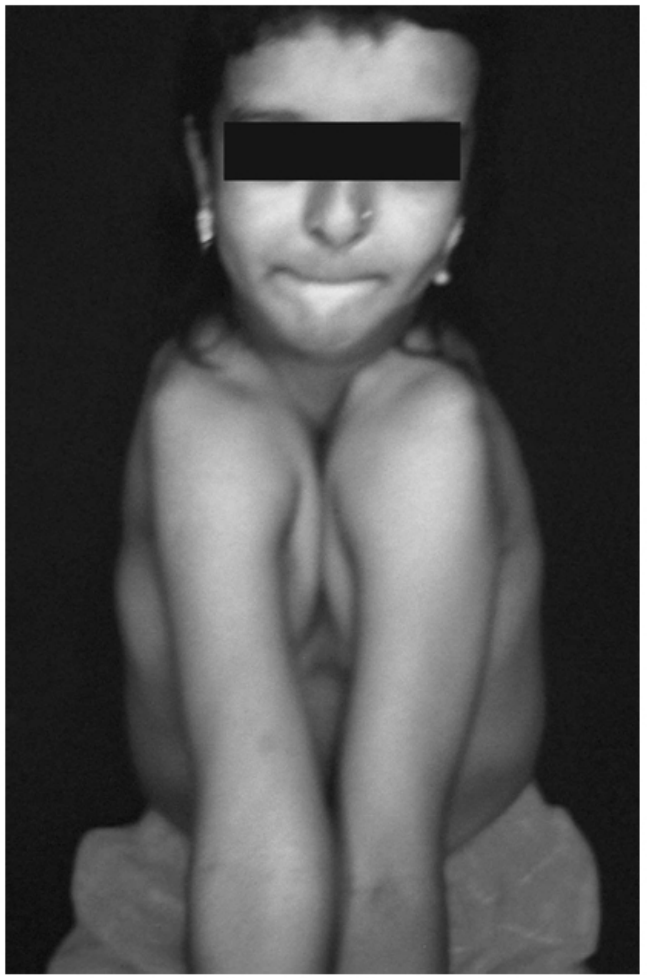




Patología humana asociada: Displasia cleidocraneal

Cr. 6p21





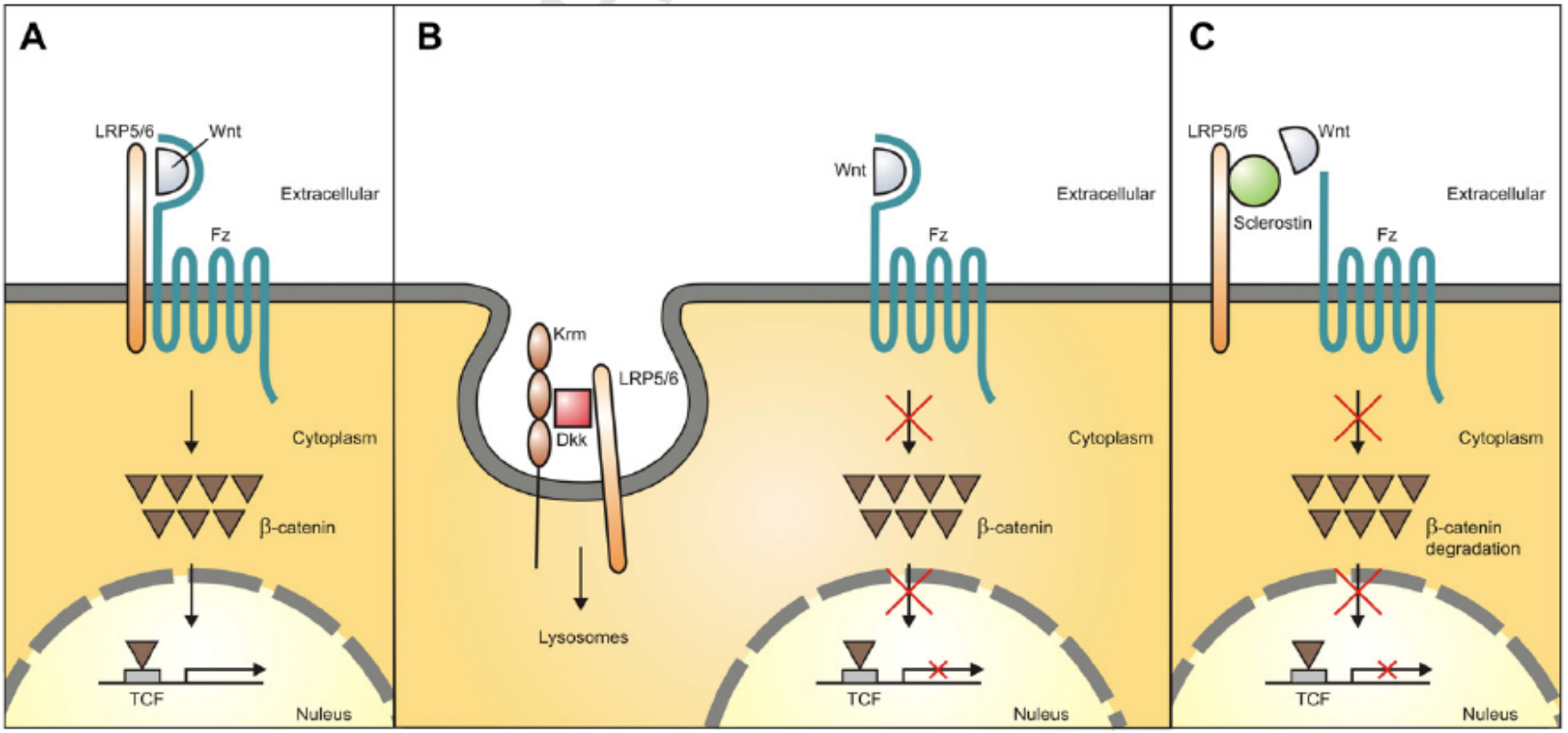


Fig. 2. The canonical wnt/β-catenin signaling pathway and its extracellular regulation. (A) Extracellular binding of wnt to the Fz–LRP5/6 receptor complex causes intracellular accumulation of β-catenin that can induce the expression of target genes after translocation to the nucleus. (B) In the presence of Dkk and Krm a tertiary protein complex can be made with LRP5/6 for internalization thus inhibiting wnt signaling as β-catenin will no longer be stabilized but will be phosphorylated and subsequently degraded. (C) The extracellular sclerostin prevents by binding to LRP5/6–Fz further signaling.

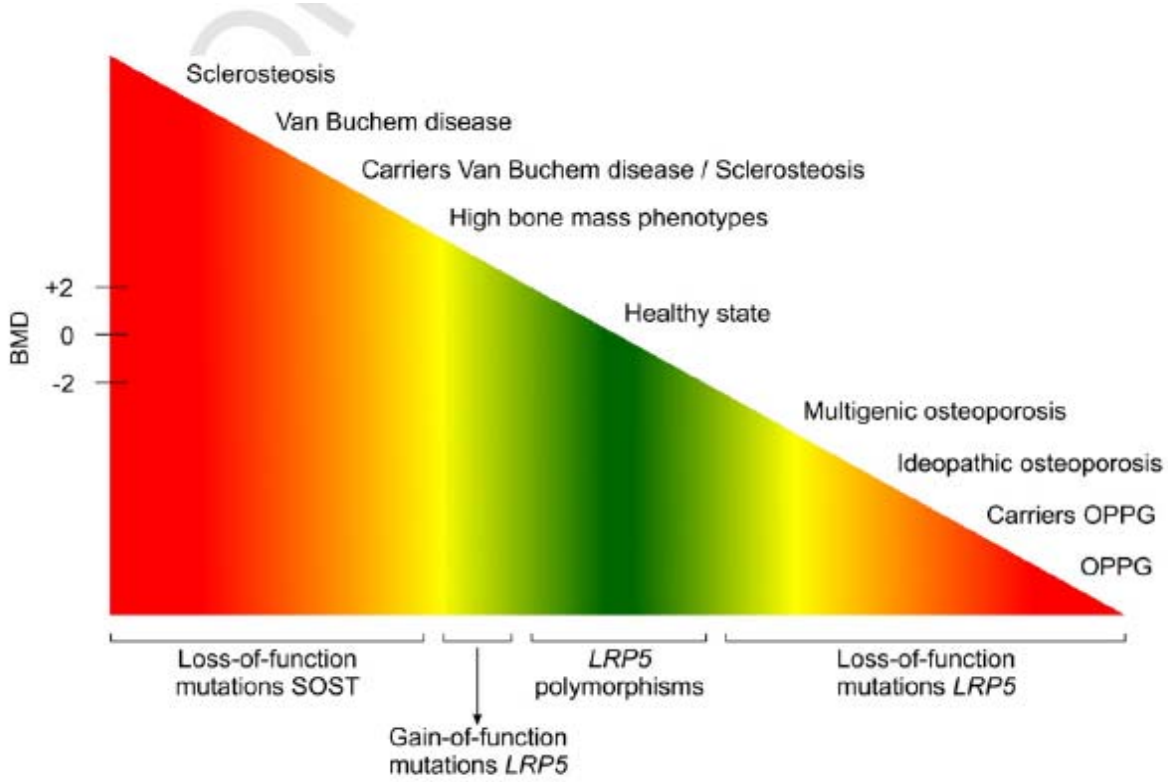


Fig. 3. Mutations or genetic variation in two components of the wnt-signaling pathway (SOST and LRP5) result in a broad spectrum of bone mineral densities.

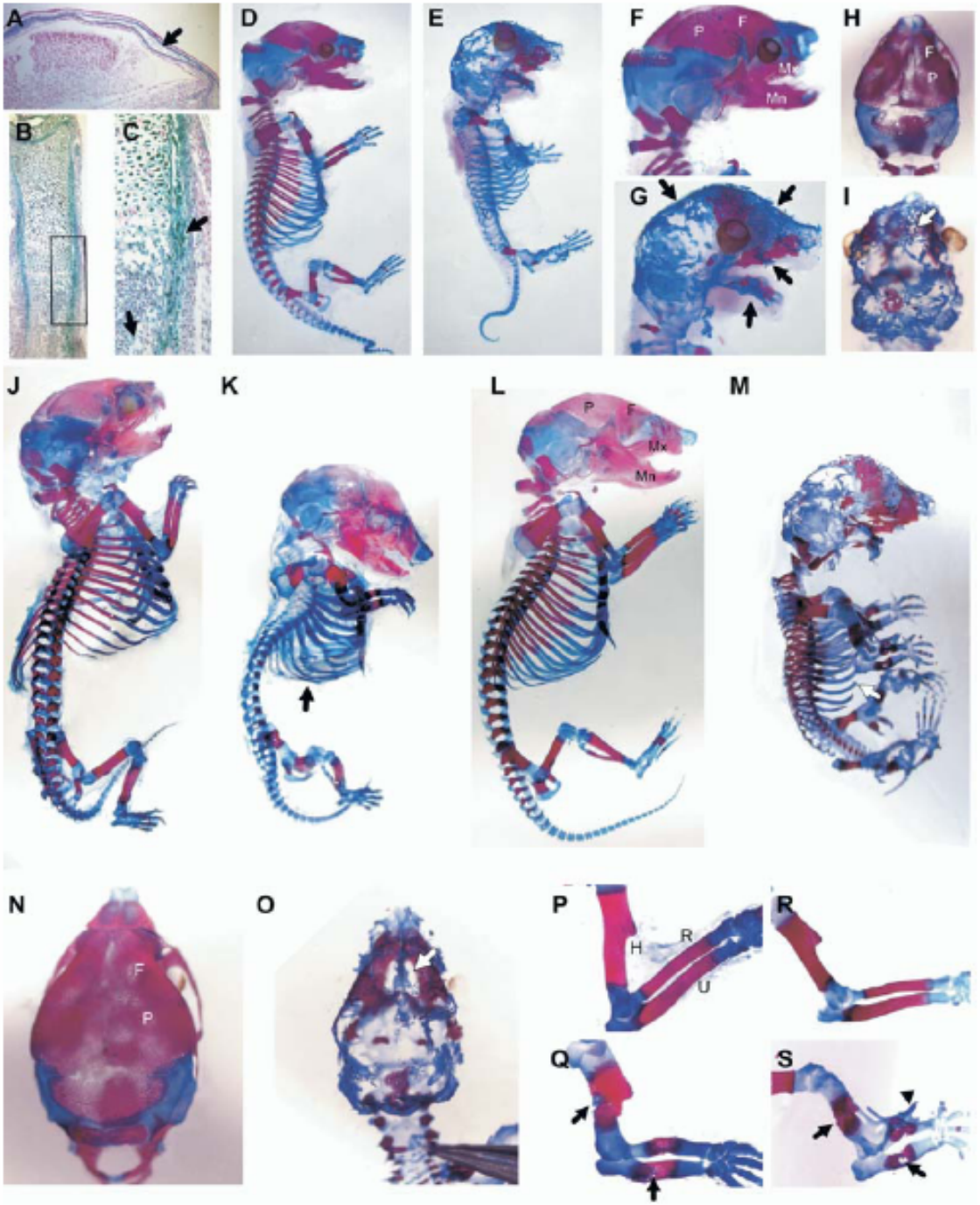


Figure 3. Inactivation of β-*catenin* during Both Intramembranous and Endochondral Ossification Led to Ectopic Cartilage Formation at the Expense of Bone Formation

(A) *LacZ* expression in the developing frontal bone (arrow) at 14.5 dpc in the *Dermo1-Cre;R26R* mouse.

(B) *LacZ* expression in both chondrocytes and perichondrium of a tibia in the *Col2a1-Cre;R26R* mouse embryo at 15.5 dpc.

(C) The boxed region in (B) is enlarged, showing *LacZ*-expressing cells (arrows) in both periosteum and primary spongiosa.

(D–S) Skeletal preparations of mouse embryos. Cartilage was stained by Alcian blue whereas bone was stained by Alizarin red. Loss of bone formation and ectopic cartilage formation are indicated by arrows. F, frontal bone; P, parietal bone; Mx, maxilla; Mn, mandible.

(D) *Catnby*$^{c/+}$*;Dermo1-Cre* embryo at 15.5 dpc.

(E) *Catnby*$^{c/c}$*;Dermo1-Cre* embryo (littermate of [D]).

(F) Enlarged head region of (D).

(G) Enlarged head region of (E).

(H) Enlarged head region of (D), dorsal view.

(I) Enlarged head region of (E), dorsal view.

(J) *Catnby*$^{c/+}$*;Col2a1-Cre* embryo at 17.5 dpc. A forelimb is shown in (P).

(K) *Catnby*$^{c/-}$*;Col2a1-Cre* embryo (littermate of [J]). A forelimb is shown in (Q).

(L) *Catnby*$^{c/+}$*;Dermo1-Cre* mouse embryo at 17.5 dpc. The dorsal view of the head is shown in (N) and a forelimb is shown in (R).

(M) *Catnby*$^{c/c}$*;Dermo1-Cre* embryo (littermate of [L]). The dorsal view of the head is shown in (O) and a forelimb is shown in (S).

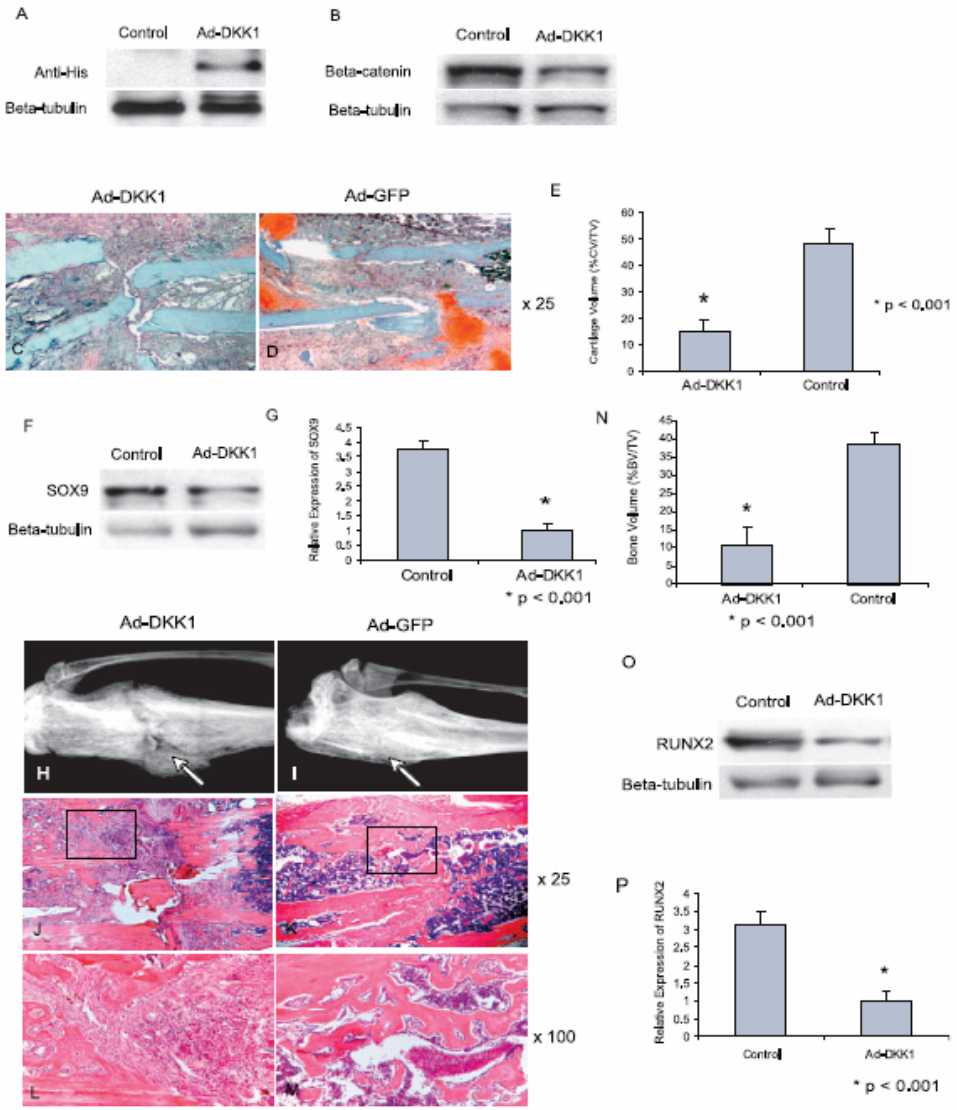


Figure 3. WNT Ligands Regulate β-Catenin during Fracture Healing

(A) Western blot analysis shows expression of DKK1 as detected by an antibody to the His tag.

(B) β-catenin was substantially down-regulated in fractures treated with DKK1.

(C and D) SO staining of fracture samples from DKK1-treated mice (C) and control mice (D) at 1 wk after fracture show that DKK1 treatment down-regulates chondrogenic differentiation. Images are magnified 25×.

(E) Histomorphometric analysis shows a down-regulation of cartilage volume (CV) at 1 wk after fracture, as a percentage of total callus tissue volume (TV), in DKK1-treated mice.

(F and G) SOX9 was also down-regulated after treatment with Ad-DKK1 at 1 wk following fracture. The expression data are consistent with our histological findings.

(H and I) Radiographic analysis from DKK1-treated mice (H) and from control mice (I), at 3 wk after fracture, shows a lack of healing in the DKK1-treated animals. Arrows indicate fracture site.

(J–M) HE staining from DKK1-treated mice (J and L) and from control mice (K and M) undifferentiated mesenchymal-like cells at the fracture site in DKK1-treated animals at 3 wk after fracture. Images (J and K) are magnified 25×; (L and M) show 100× magnifications of the area shown in the box in the lower-magnification images.

(N) Assay of bone volume (BV) as a percentage of total callus tissue volume (TV) shows a significant decrease in bone regeneration after DKK1 treatment.

(O and P) RUNX2 was also significantly down-regulated in DKK1-treated mice, suggesting an inhibition of osteoblastic differentiation.

doi:10.1371/journal.pmed.0040249.g003

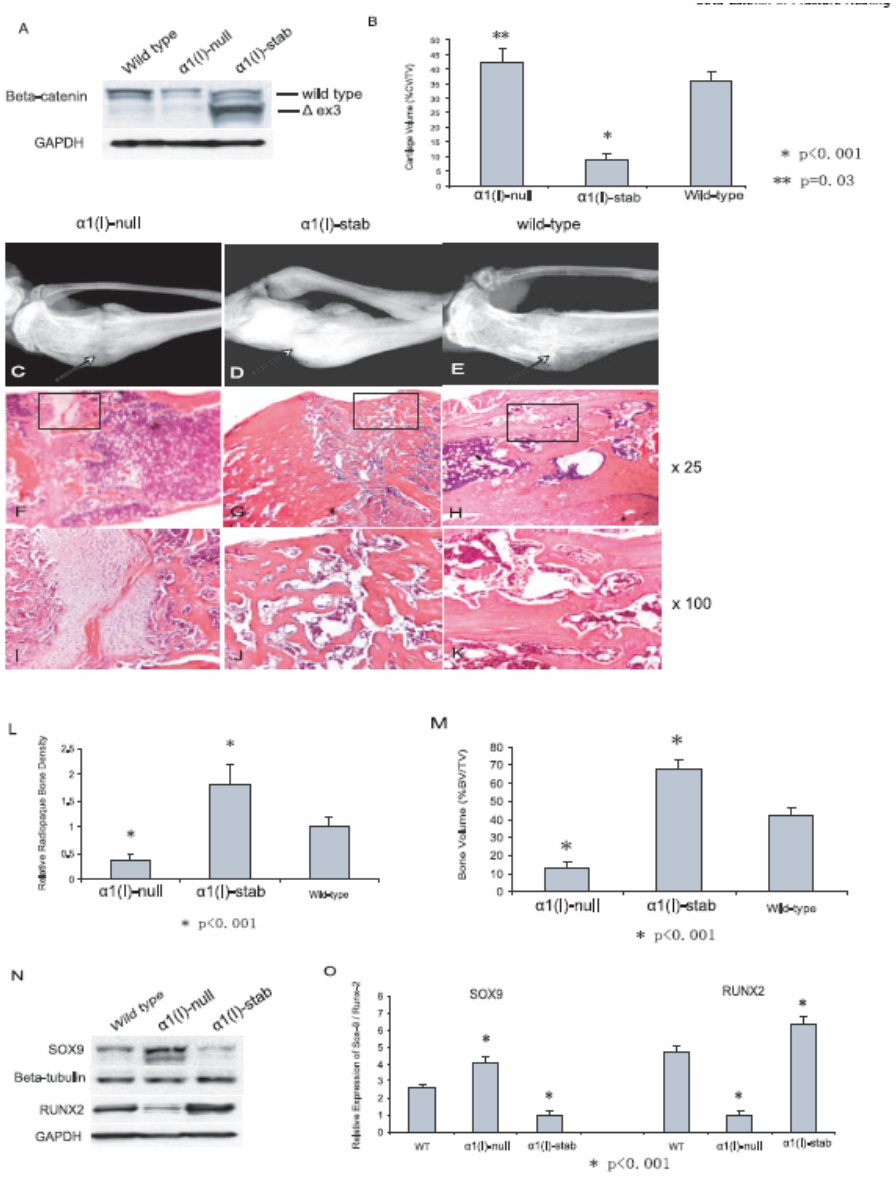


Figure 4. β-Catenin Acts to Regulate Bone Formation in Mice Expressing Osteoblast-Specific β-Catenin Null or Stabilized Alleles

(A) Western blot analysis shows that β-catenin was regulated in the bone as expected in *α1(I)-Catnb*^{null} and *α1(I)-Catnb*^{stab} (*α1(I)-null* and *α1(I)-stab*, respectively) mice.

(B) Histomorphometric analysis of calluses at 1 wk following fracture, as indicated by cartilage volume (CV) as a percentage of total callus tissue volume (TV).

(C–E) Radiographic analysis from *α1(I)-Catnb*^{null} mice (C), from *α1(I)-Catnb*^{stab} mice (D), and from wild-type littermate mice (E) at 3 wk after fracture. Arrows indicate fracture site.

(F–K) HE staining from *α1(I)-Catnb*^{null} mice (F and I), from *α1(I)-Catnb*^{stab} mice (G and J), and from wild-type mice (H and K) shows that bone healing was inhibited in *α1(I)-Catnb*^{null} mice at 3 wk after fracture, with remaining cartilage at the fracture site. *α1(I)-Catnb*^{stab} mice showed an accelerated fracture repair with abundant new bone tissue formed. Images (F, G, and H) are 25× magnifications; (I, J, and K) are 100× magnifications of the areas shown in the box in the lower-magnification images.

(L) Relative radiopaque bone density at the fracture site shows decreased bone density in *α1(I)-Catnb*^{null} mice and increased bone density in *α1(I)-Catnb*^{stab} mice.

(M) Assay of bone volume (BV) as a percentage of total callus tissue volume (TV) shows that *α1(I)-Catnb*^{null} mice displayed inhibition of fracture healing, whereas osteoblast-specific β-catenin activation in *α1(I)-Catnb*^{stab} mice enhanced bone healing.

(N and O) Regulation of SOX9 at 1 wk and RUNX2 at 3 wk following fracture in *α1(I)-Catnb*^{null}, *α1(I)-Catnb*^{stab}, and wild-type mice.

doi:10.1371/journal.pmed.0040249.g004

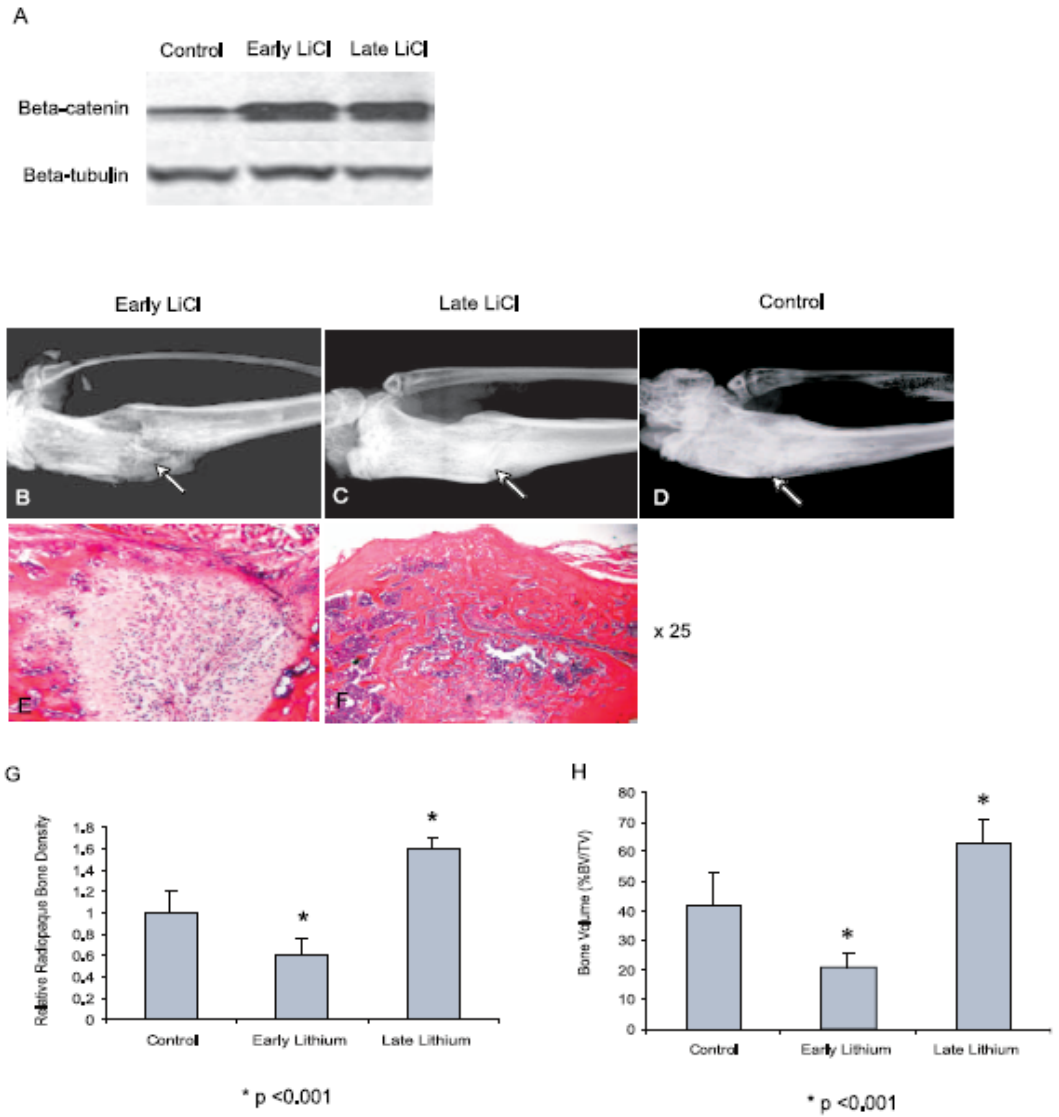


Figure 5. Lithium Treatment Regulates Bone Mass at the Fracture Site

Mice were treated with lithium starting either 2 wk before the fracture (early treatment) or 4 d after the fracture (late treatment).

(A) β-catenin increased 3 wk after fracture in mice receiving either early or late lithium treatment.

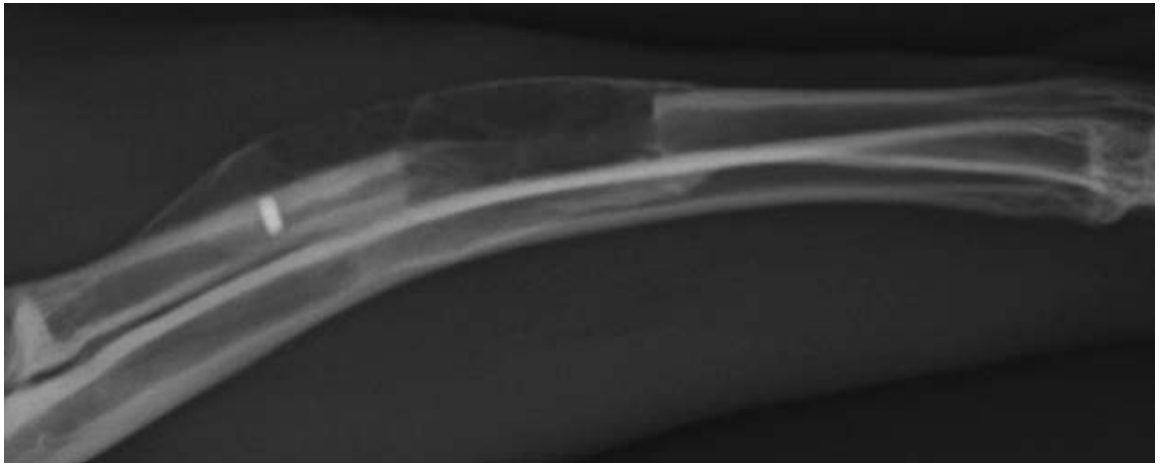
(B–D) Radiographic analysis from mice receiving early lithium treatment (B), late lithium treatment (C), or NaCl as a control (D), show that lithium enhanced fracture healing only when given late. Arrows indicate the fracture site.

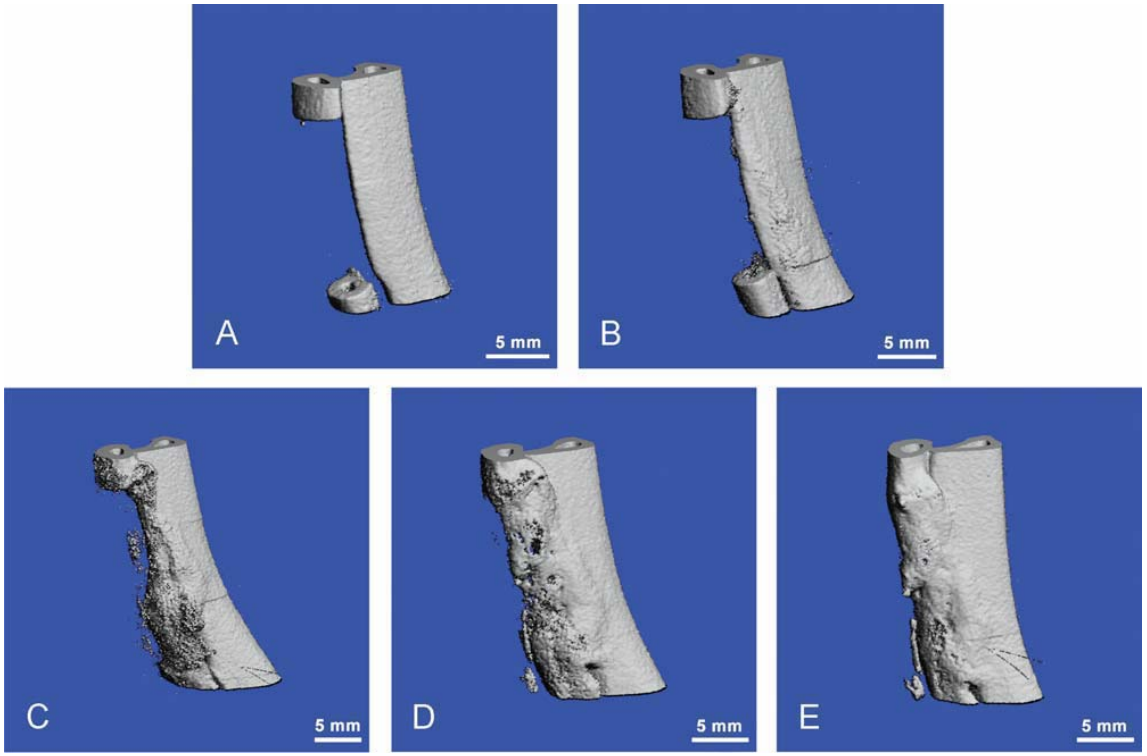
(E and F) HE staining from mice receiving early or late lithium treatments, respectively (25×). There is immature mesenchymal tissue at the fracture site in (E), and large amounts of bone in (F).

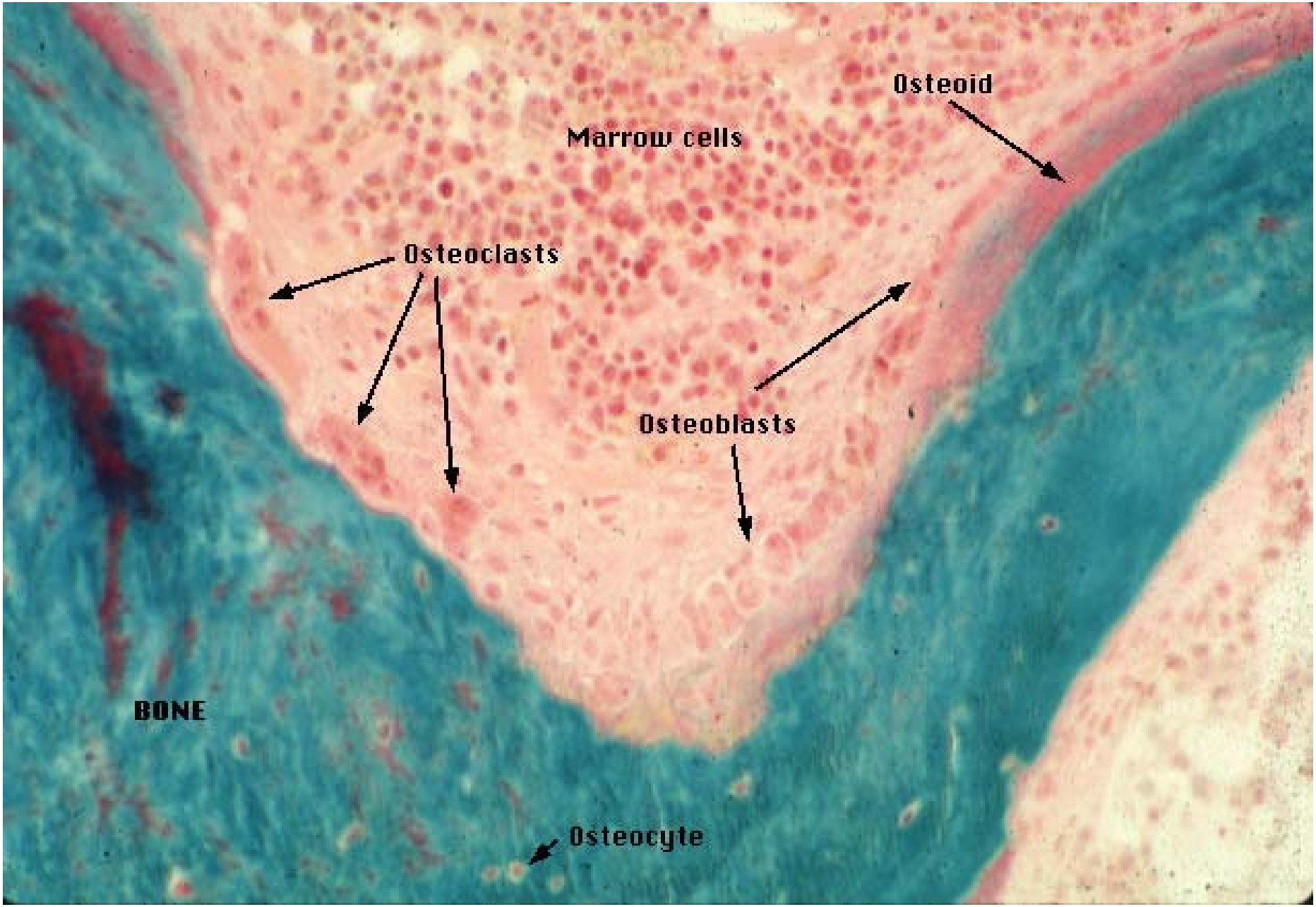
(G) Relative radiopaque bone density results show that early and late treatment have opposite effects on fracture healing.

(H) Histomorphometric analysis on bone volume (BV) as a percentage of total callus tissue volume (TV), showing that pharmacologic activation of β-catenin after healing cells become committed to the osteoblast lineage could improve healing, while treatment at earlier time points inhibited fracture repair.

doi:10.1371/journal.pmed.0040249.g005

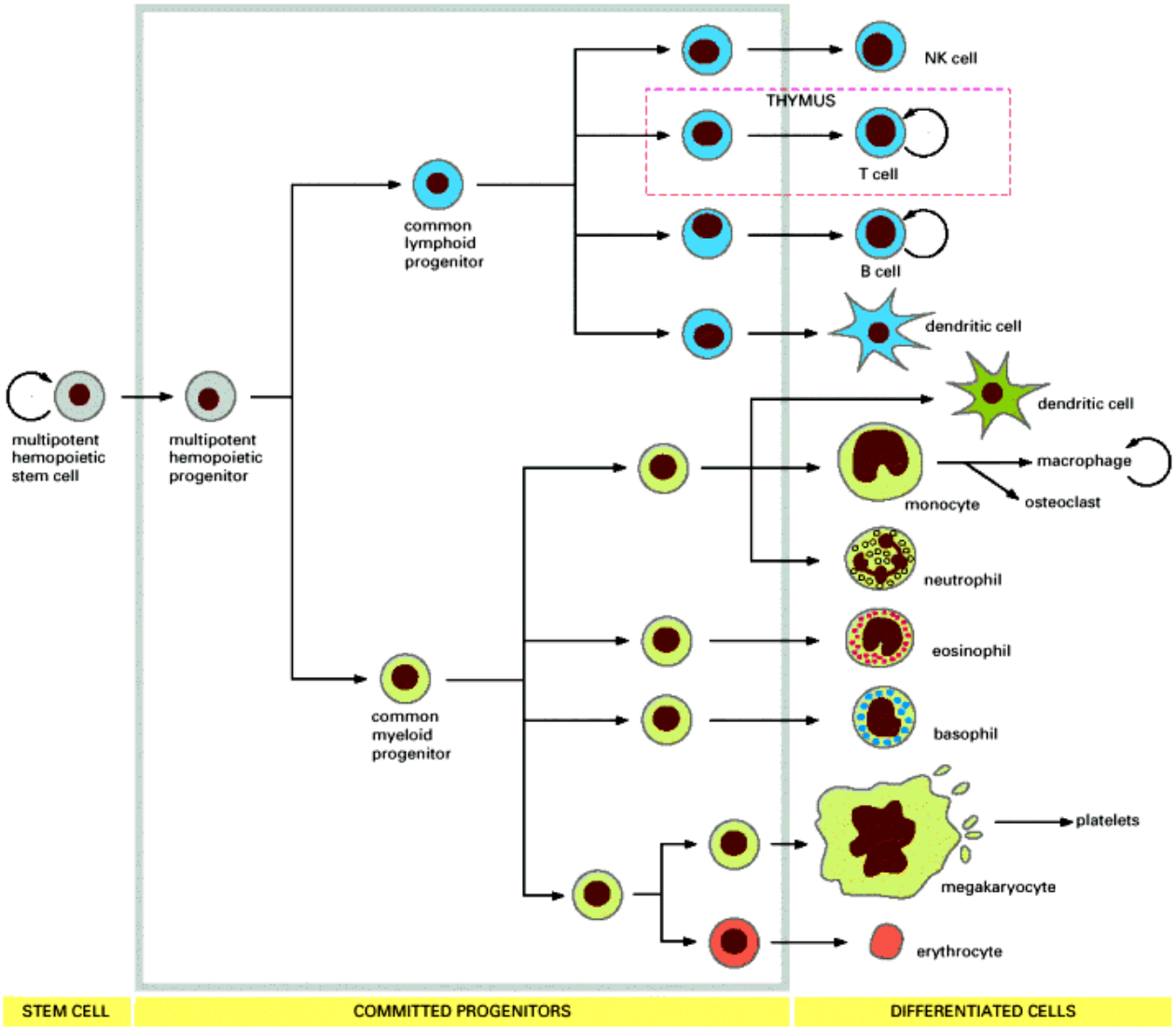



A
5 mm
B
5 mm
C
5 mm
D
5 mm
E
5 mm


Osteoid
Marrow cells
Osteoclasts
Osteoblasts
BONE
Osteocyte

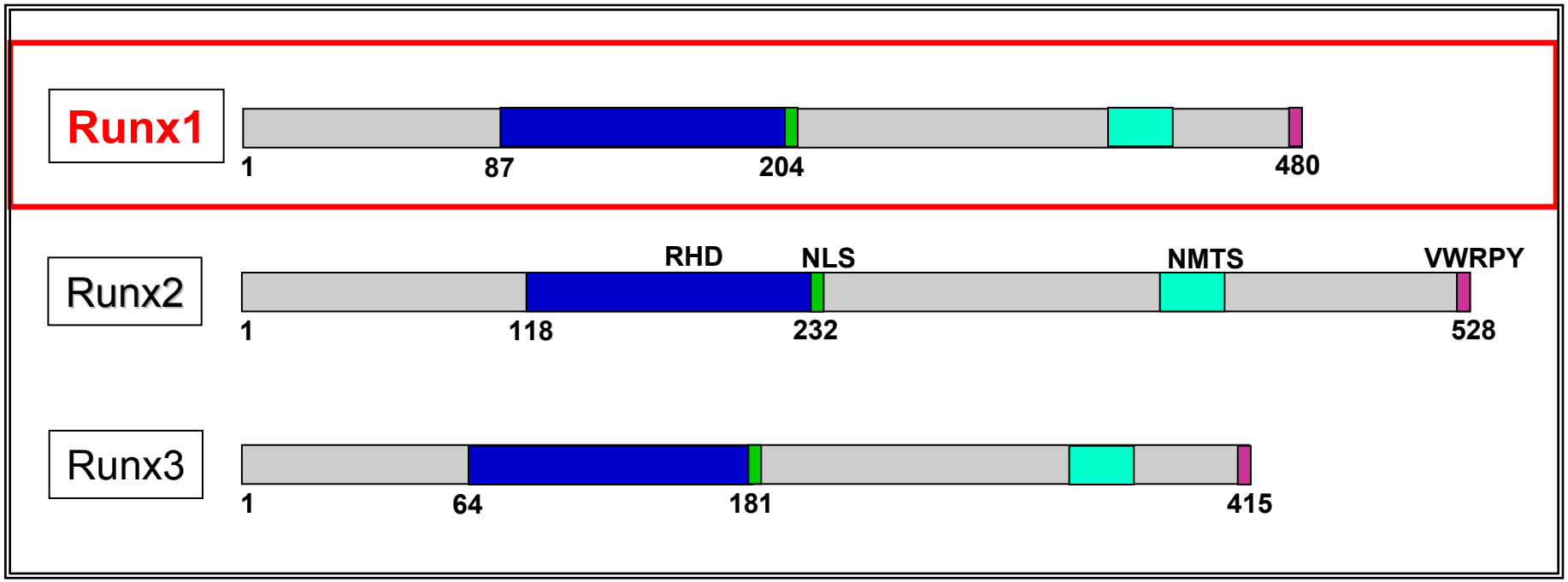
MECANISMOS MOLECULARES DE LA DIFERENCIACIÓN CELULAR

MODELO DE FORMACIÓN DE LAS CÉLULAS DE LA SANGRE



EL FACTOR DE TRANSCRIPCIÓN RUNX1

DOMINIOS FUNCIONALES DE LAS PROTEINAS RUNX



RHD — ***Runt Homology Domain*** ***(DNA binding, Protein-Protein interaction)***

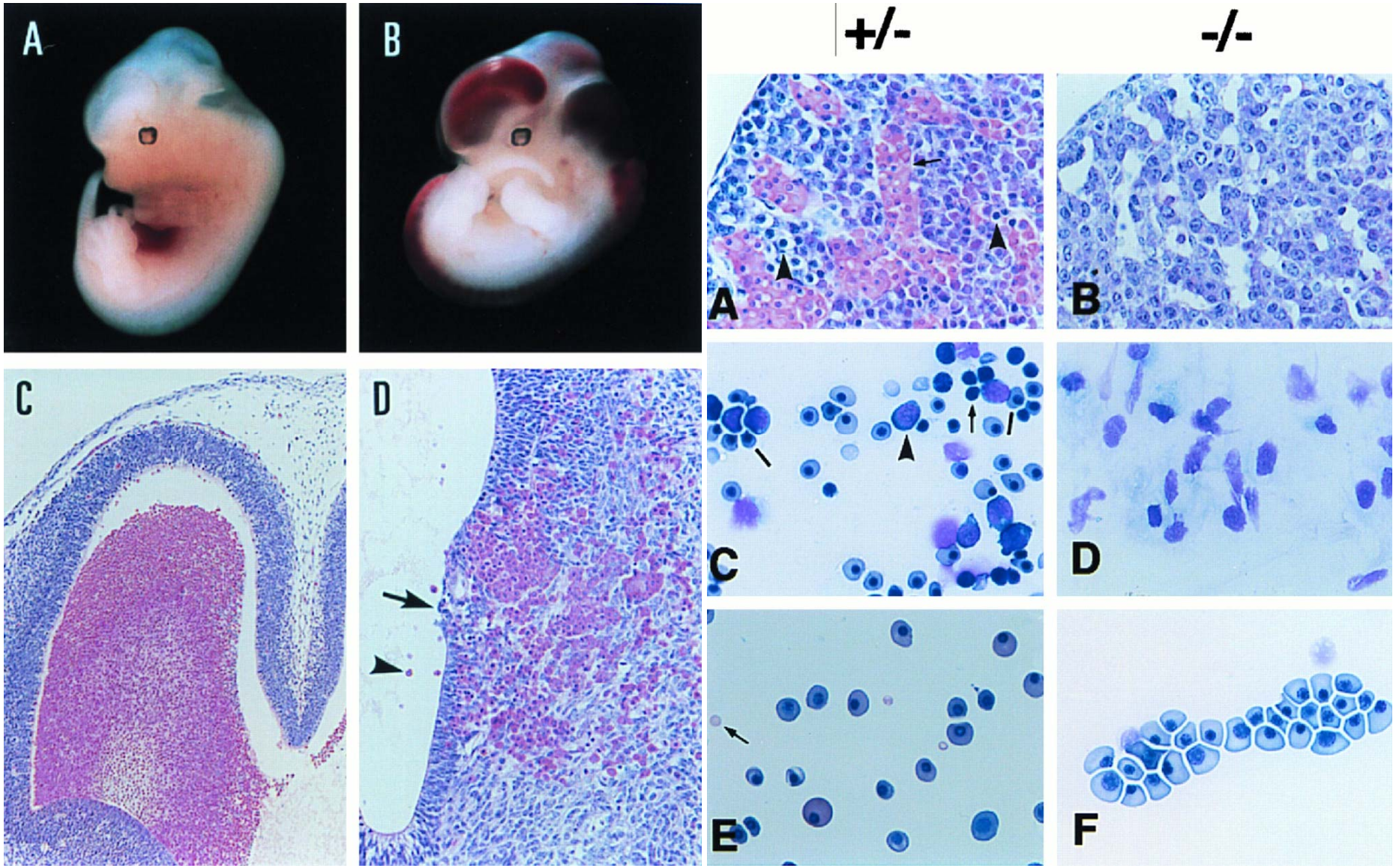
NSL — ***Nuclear Signaling Localization***

NMTS — ***Nuclear Matriz Targeting Signal*** ***(PST-Rich Domain)***

VWRPY — **Secuencia conservada de aminoácidos** ***(Groucho/TLE)***

GENES REGULADOS POR RUNX1

CATEGORY	*REFERENCE*
Cytokines	
-- Granulocyte-macrophage colony stimulating factor (GM-CSF).....	[Takahashi et al., 1995]
-- Interleukin-3 (IL-3)	[Cameron et al., 1994]
-- Macrophage inflammatory protein 1-α (MIP-1α)	[Bristow and Shore, 2003]
Cell surface differentiation markers	
- T cell receptor (TCR) α, β, δ, γ subunits.....	[Hallberg et al., 1992; Prosser et al., 1992; Redondo et al., 1992] [Giese et al., 1995] [Zhang et al., 1994]
- Macrophage colony stimulating factor-receptor 1 (M-CSF-R1).....	[Ji et al., 1998]
- Transforming growth factor β receptor-1 (TGFβ-R1).....	[Taniuchi et al., 2002]
- Cell surface glycoprotein CD4, CD3ε, CD36.....	[Puig-Kroger et al., 2003]
- Cell surface glycoprotein CD-11a integrin.....	[Pardali et al., 2000]
- Immunoglobulin μ heavy chain (Igα).....	[Pardali et al., 2000]
- Immunoglobulin μ heavy chain (IgH).....	
B-cell specific genes	
- Granzyme B.....	[Babichuk and Bleackley, 1997]
- B cell specific tyrosine kinase.....	[Libermann et al., 1999]
- λ5	[Martensson et al., 2001]
Myeloid specific genes	
- Mouse mast cell protease-6 (MMCP-6).....	[Ogihara et al., 1999]
- Myeloperoxidase MPO).....	[Britos-Bray and Friedman, 1997]
- Neutrophil elastase	[Nuchprayoon et al., 1994]
- P14(ARF).....	[Linggi et al., 2002]



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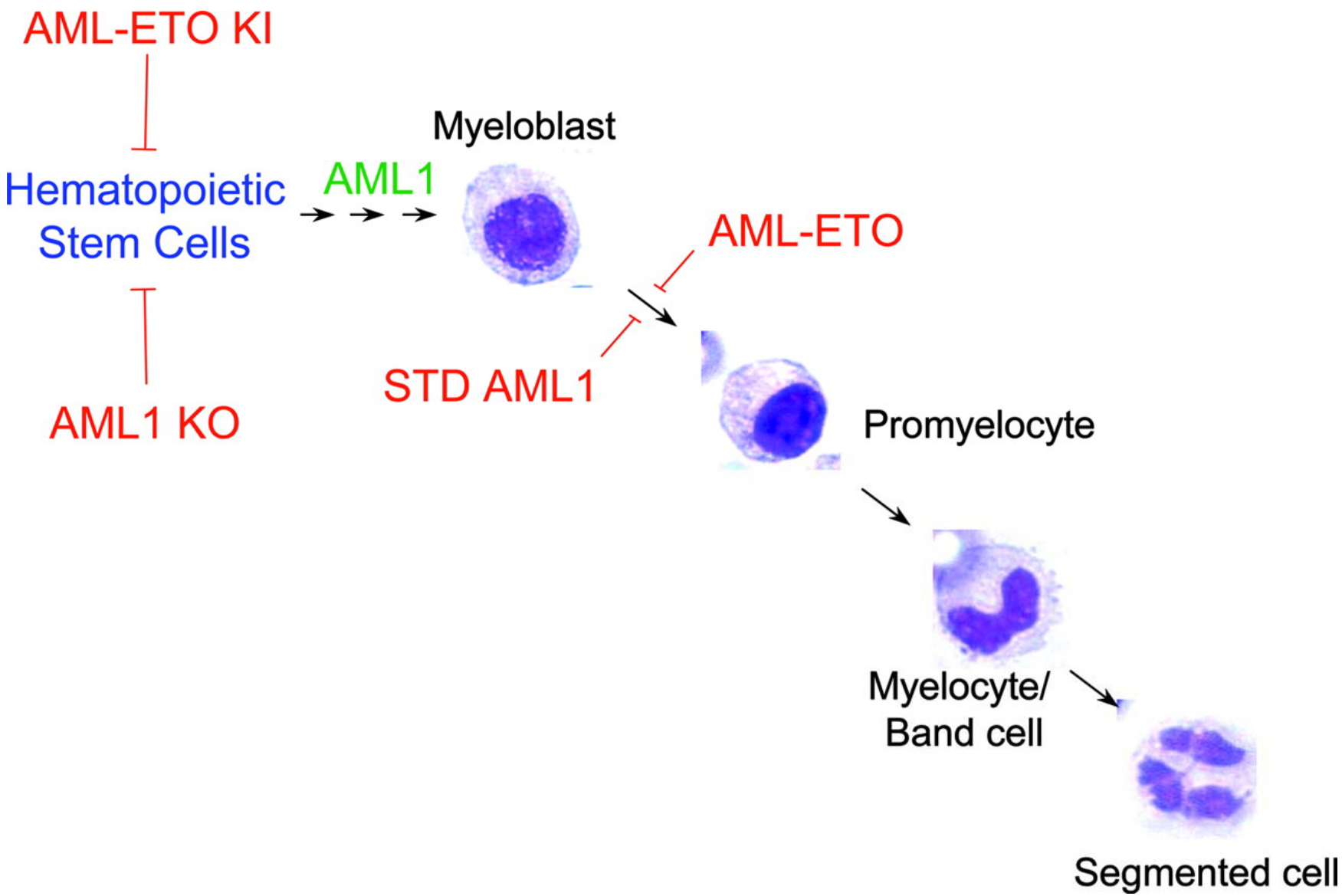
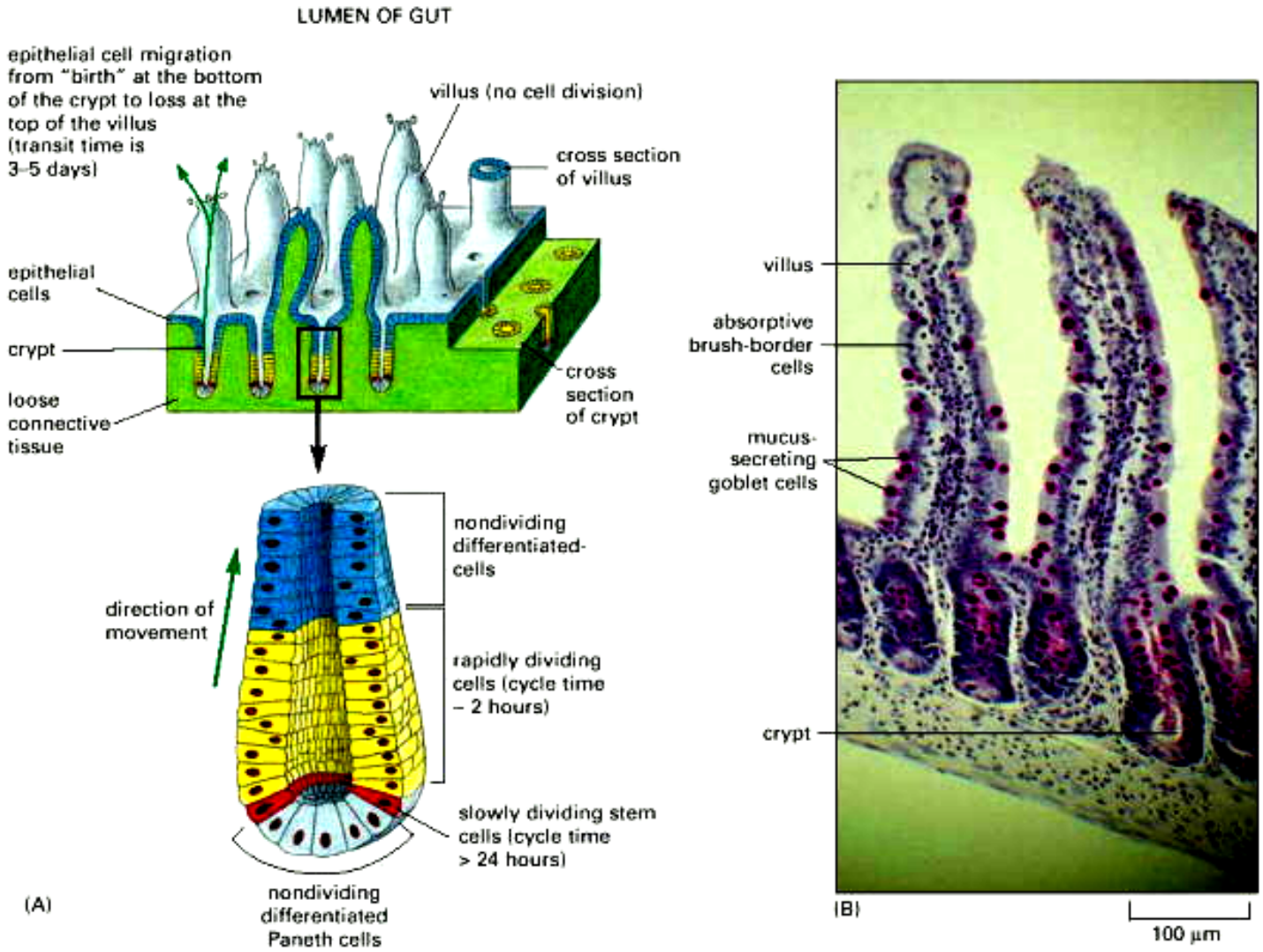

AML-ETO KI
Hematopoietic
Stem Cells
AML1 KO
AML1
Myeloblast
AML-ETO
STD AML1
Promyelocyte
Myelocyte/
Band cell
Segmented cell

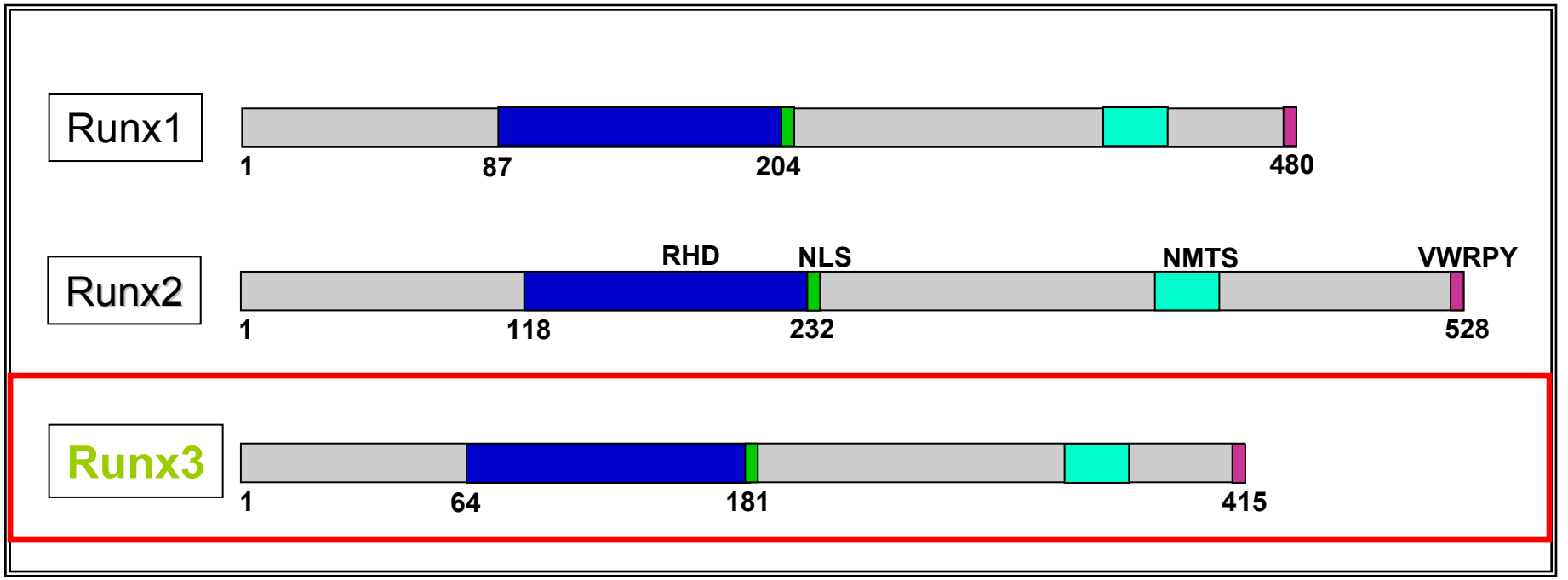
MECANISMOS MOLECULARES DE LA DIFERENCIACIÓN CELULAR

MODELO DE FORMACIÓN DEL SISTEMA GASTRO-INTESTINAL



EL FACTOR DE TRANSCRIPCIÓN RUNX3

DOMINIOS FUNCIONALES DE LAS PROTEINAS RUNX



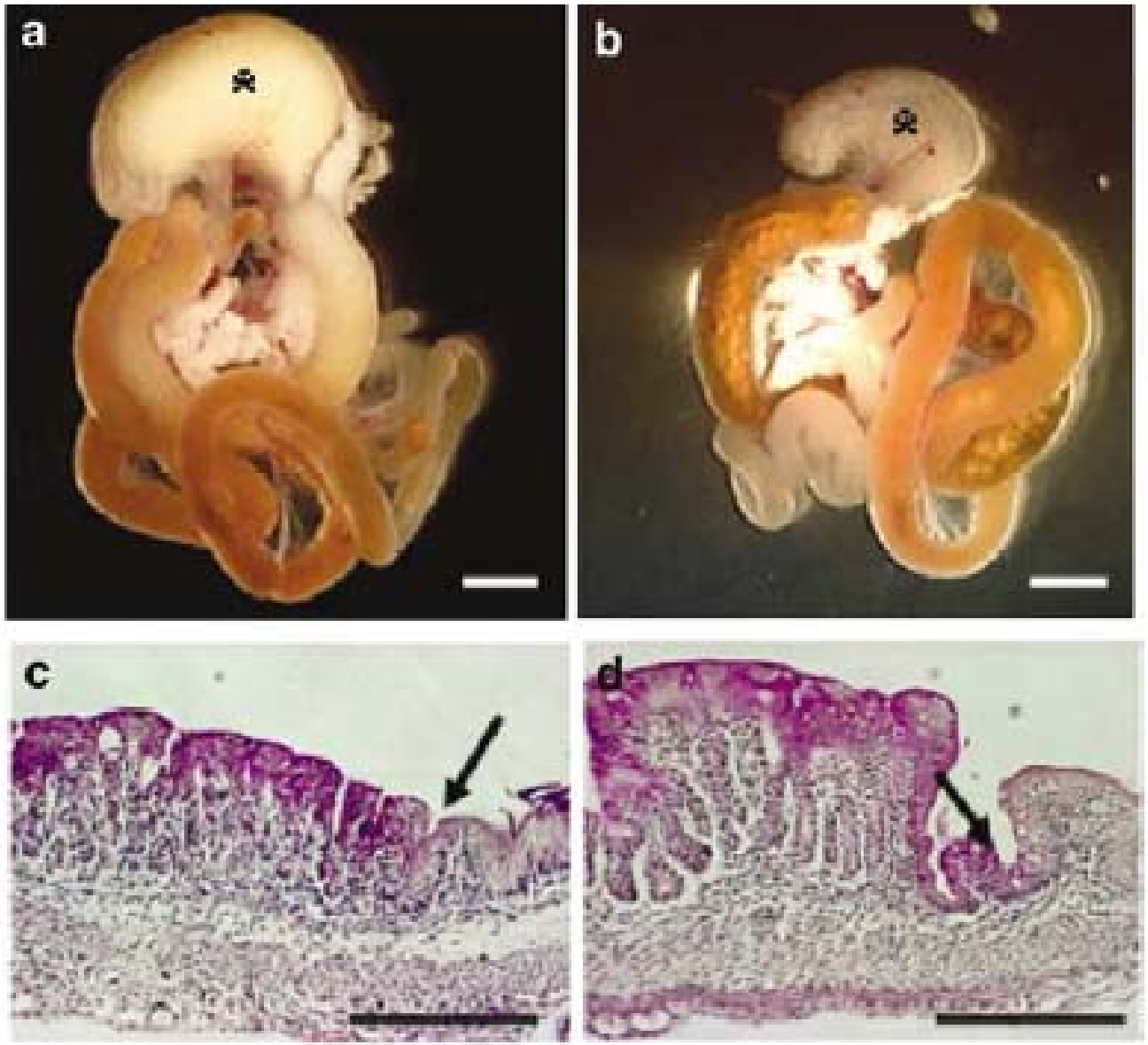
RHD — ***Runt Homology Domain*** ***(DNA binding, Protein-Protein interaction)***

NSL — ***Nuclear Signaling Localization***

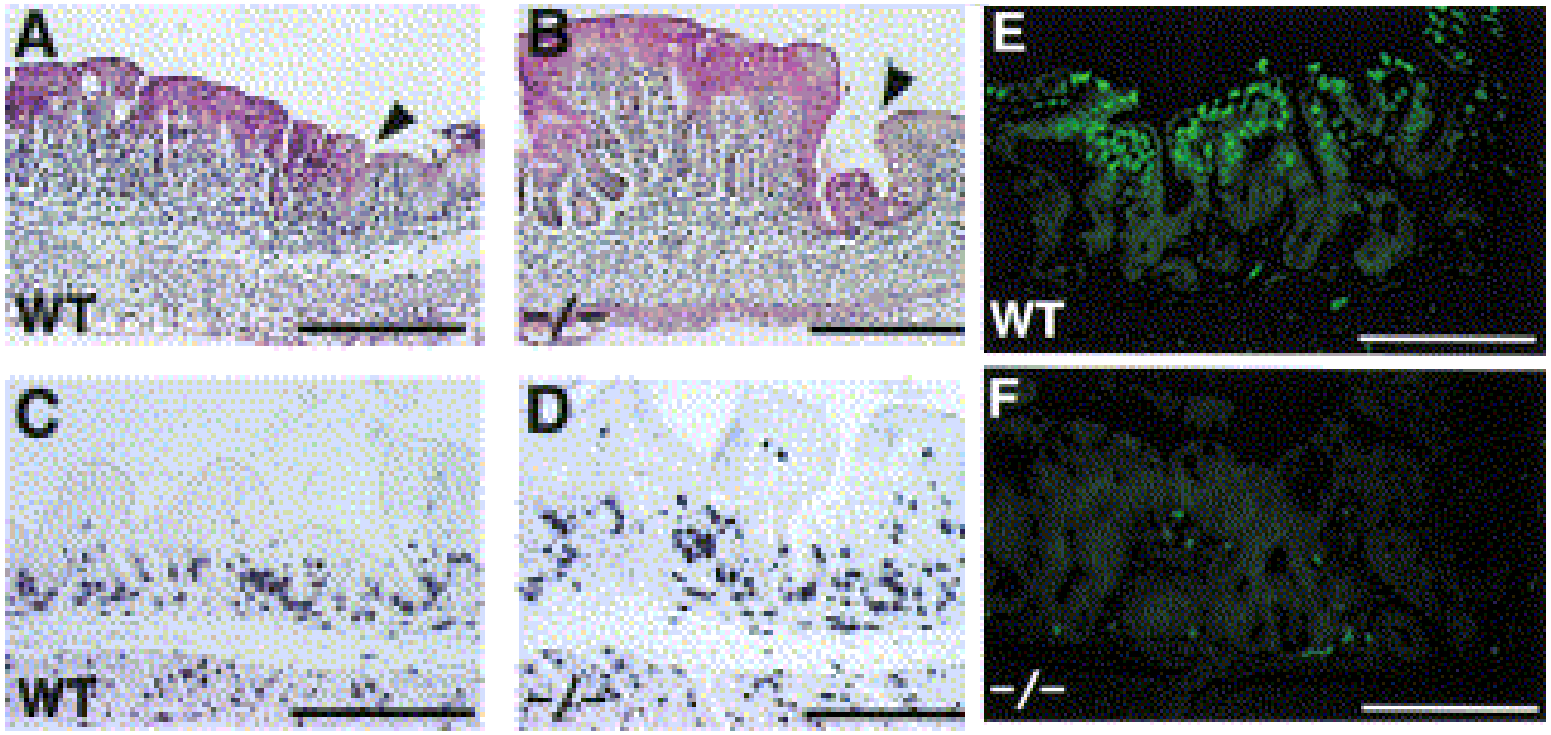
NMTS — ***Nuclear Matriz Targeting Signal*** ***(PST-Rich Domain)***

VWRPY — **Secuencia conservada de aminoácidos** ***(Groucho/TLE)***

WT RUNX3 -/-



WT RUNX3 -/-



MARCADOR DE PROLIFERACION CELULAR

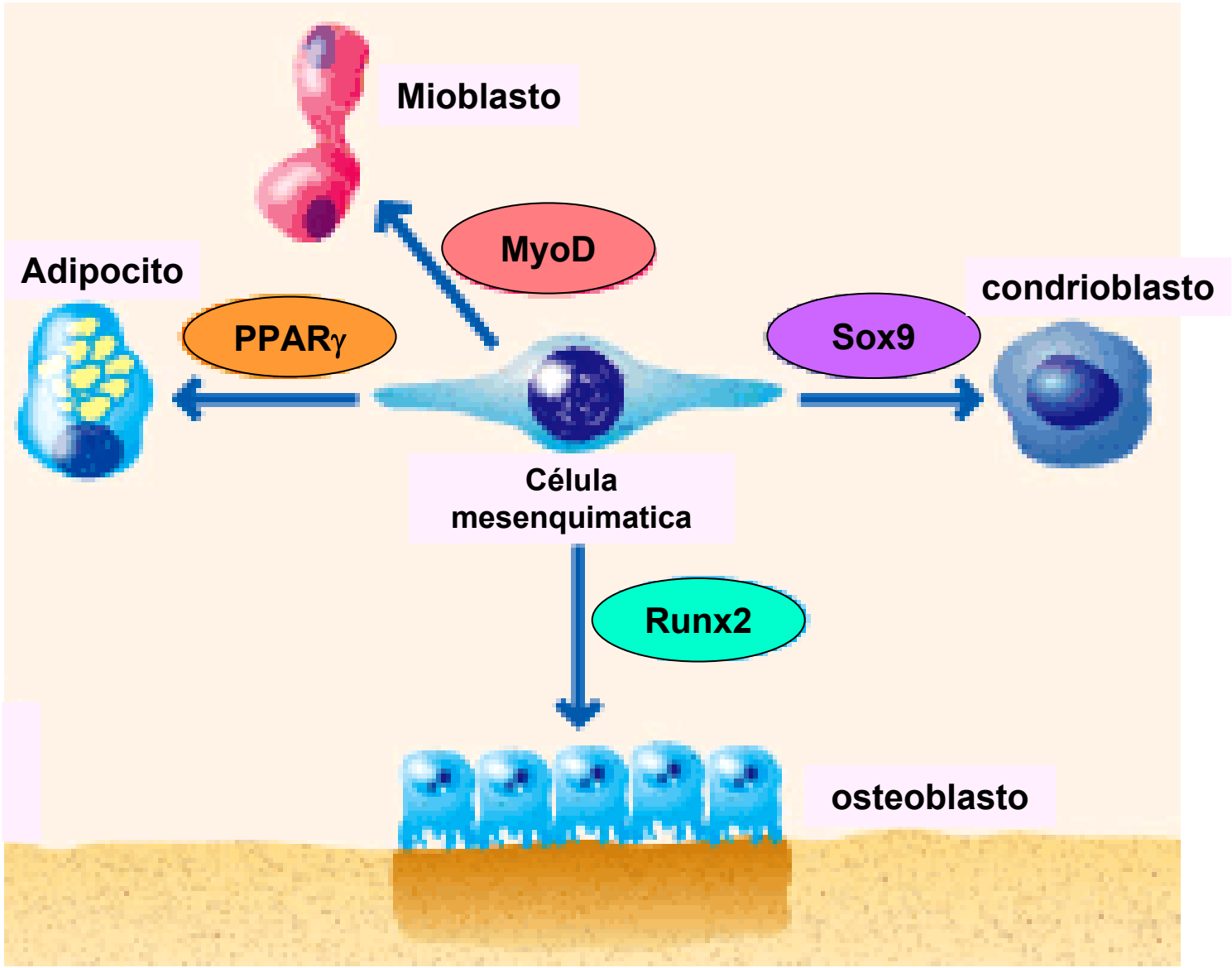
MARCADOR DE APOPTOSIS

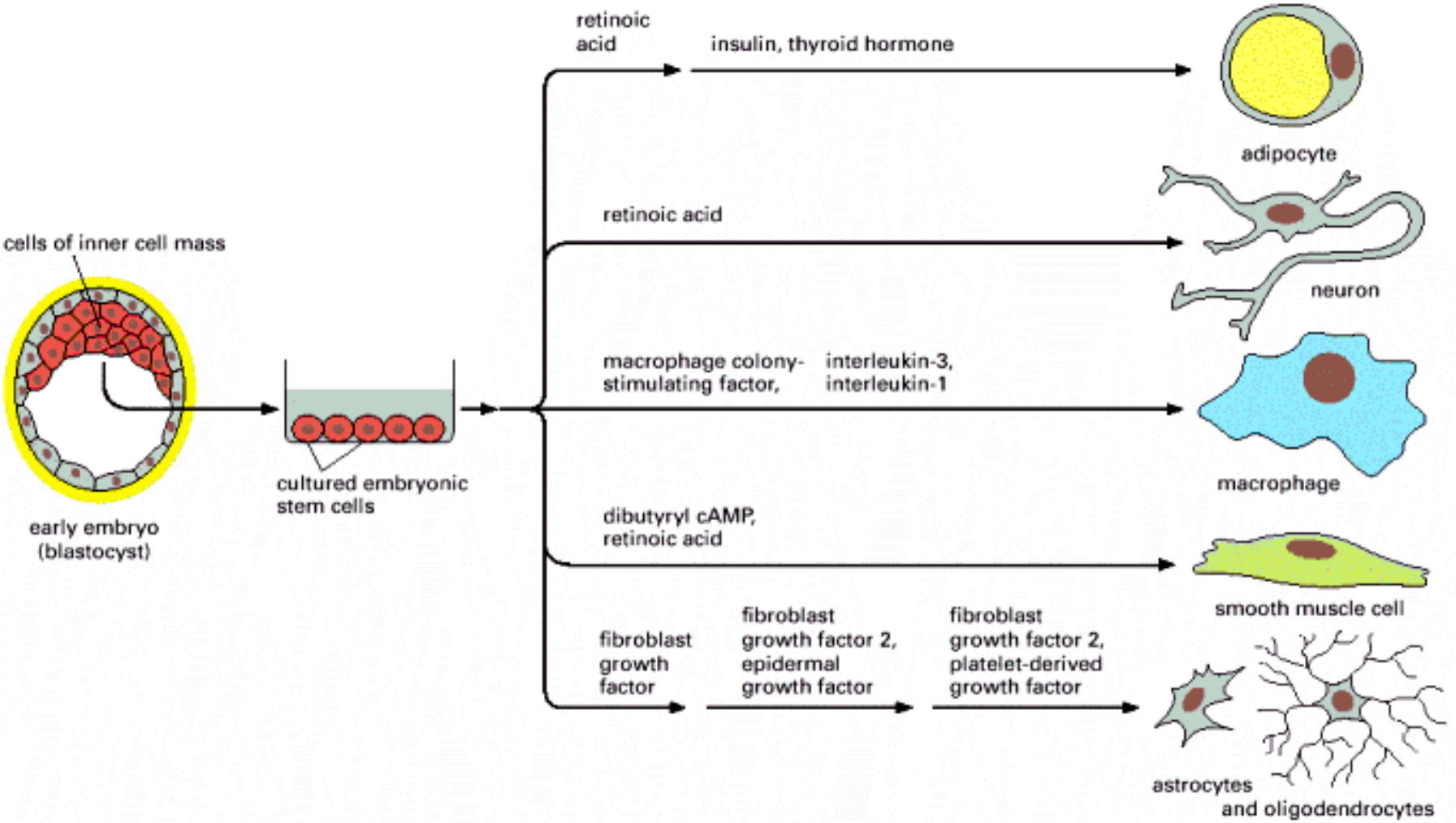
FAMILIA DE PROTEINAS RUNX

Factores de Transcripción Familia Runx	Función esencial propuesta	Efecto observado en ratones con inactivación homocigótica	Patología asociada a su deficiencia en humanos
Runx1	Hematopoyesis	Muerte fetal por falla en hematopoyesis (1)	Leucemia (2) (mieloide)
Runx3	Neurogénesis Timogénesis Desarrollo del tracto gastrointestinal	Desarrollo anormal del epitelio gástrico y de la raíz ganglionar dorsal (3)	Cáncer Gástrico (4)
Runx2	**Osteogénesis Condrogénesis**	**Ratones de termino, pero inviables debido a la ausencia de huesos (5)**	**Displasia Cleidocraneal (6)**

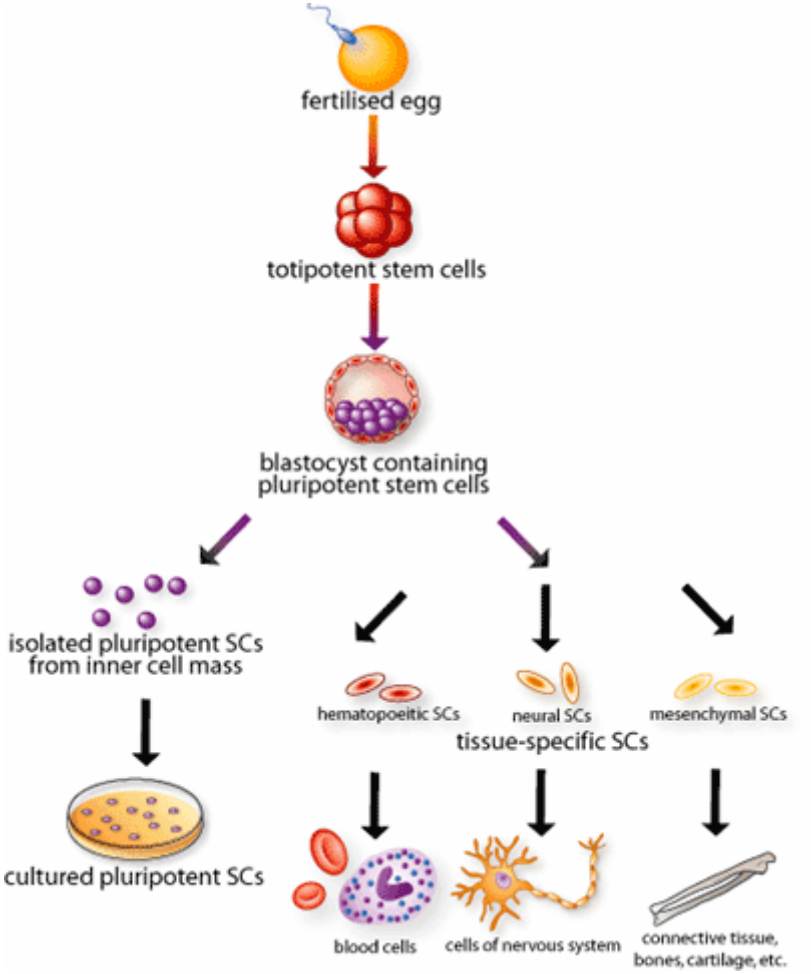
Ref.: (1) Wang y col., 1996; (2) Okuda y col., 1996; (3) Levanon y col., 2002; (4) Li y col., 2002;
(5) Komori y col., 1997; (6) Otto y col., 1997.

STEM CELL
TERAPIA CELULAR
BASADA EN CELULAS
CON POTENCIAL DE DIFERENCIACIÓN

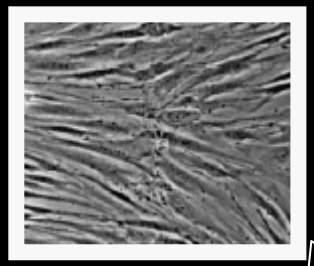

Mioblasto
MyoD
Adipocito
PPARγ
condrioblasto
Sox9
Célula
mesenquimatica
Runx2
osteoblasto

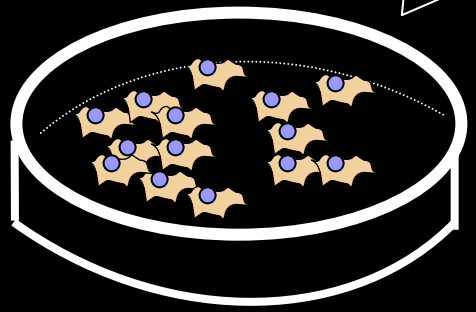

cells of inner cell mass
early embryo
(blastocyst)
cultured embryonic
stem cells
retinoic
acid
insulin, thyroid hormone
adipocyte
retinoic acid
neuron
macrophage colony-
stimulating factor,
interleukin-3,
interleukin-1
macrophage
dibutyryl cAMP,
retinoic acid
smooth muscle cell
fibroblast
growth
factor
fibroblast
growth factor 2,
epidermal
growth factor
fibroblast
growth factor 2,
platelet-derived
growth factor
astrocytes
and oligodendrocytes

Aislamiento de stem cell embrionarias y diferenciación celular para terapia de reemplazo de células dañadas en tejidos específicos



Experimento de Zuk et al. Tissue Engineering 7 : 211-228, 2001





Células adherentes mononucleadas obtenidas de tejido adiposo

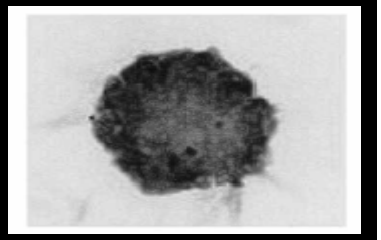
Estímulos de diferenciación específicos

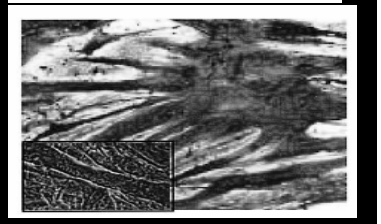
condrocitos

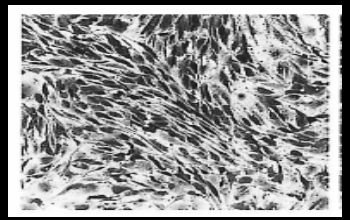
osteocitos

miocitos

adipocitos







linajes mesenquimales

Aislamiento y diferenciación de células troncales de tejidos en adultos y terapia celular