

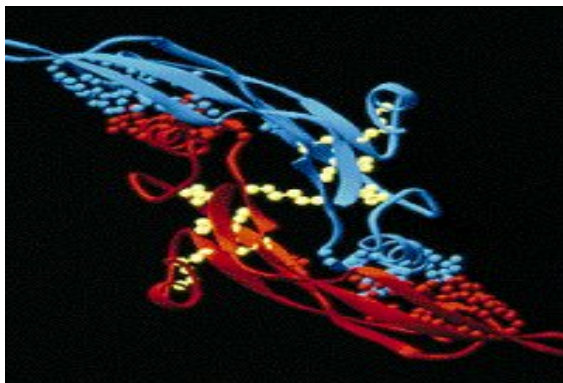
"Mecanismos de acción de la citocina TGF- β "

Marina Macías Silva

Departamento de Biología Celular y Desarrollo
Instituto de Fisiología Celular, UNAM

La Superfamilia del Factor de Crecimiento Transformante- β (TGF- β)

- TGF- β s
- Activinas
- BMPs



Descubrimiento del TGF- β



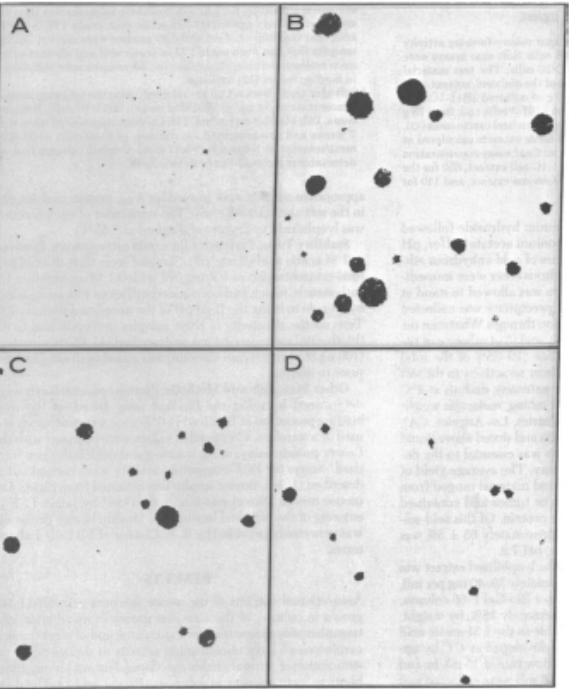
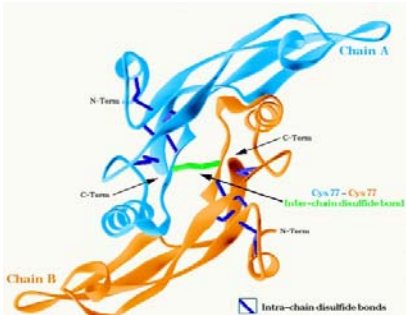
Dr. Anita B. Roberts †
(NIH, Bethesda, USA)

Transforming growth factors: Isolation of polypeptides from virally and chemically transformed cells by acid/ethanol extraction

(sarcoma growth factors/cell transformation/soft agar growth/murine sarcoma virus)

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Laboratories of *Chemoprevention and †Viral Carcinogenesis, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20205



Extractos
ácido/etanol de
células cultivadas
3B11-1C (células de
sarcoma de ratón)

Fibroblastos
de riñón de rata:
la clona 49F

FIG. 1. Soft agar growth of normal rat kidney fibroblasts. Clone 49F cells were plated in 0.3% agar and stained according to Schaeffer and Friend (13). (A) Untreated cells; (B-D) cells treated with serial 1:3 dilutions (200 µg of protein per ml in B) of the acid/ethanol extract of the cultured 3B11-1C cells. Note that both the number of colonies and the size of the colonies decrease with dilution. (x30.)

Mink Lung epithelial cells = Mv1Lu cells

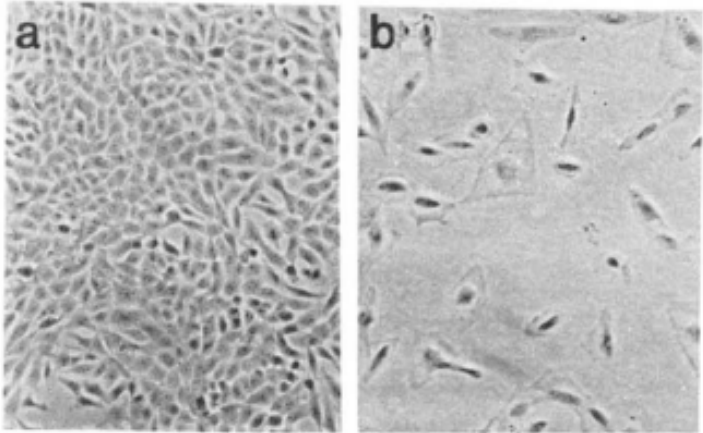
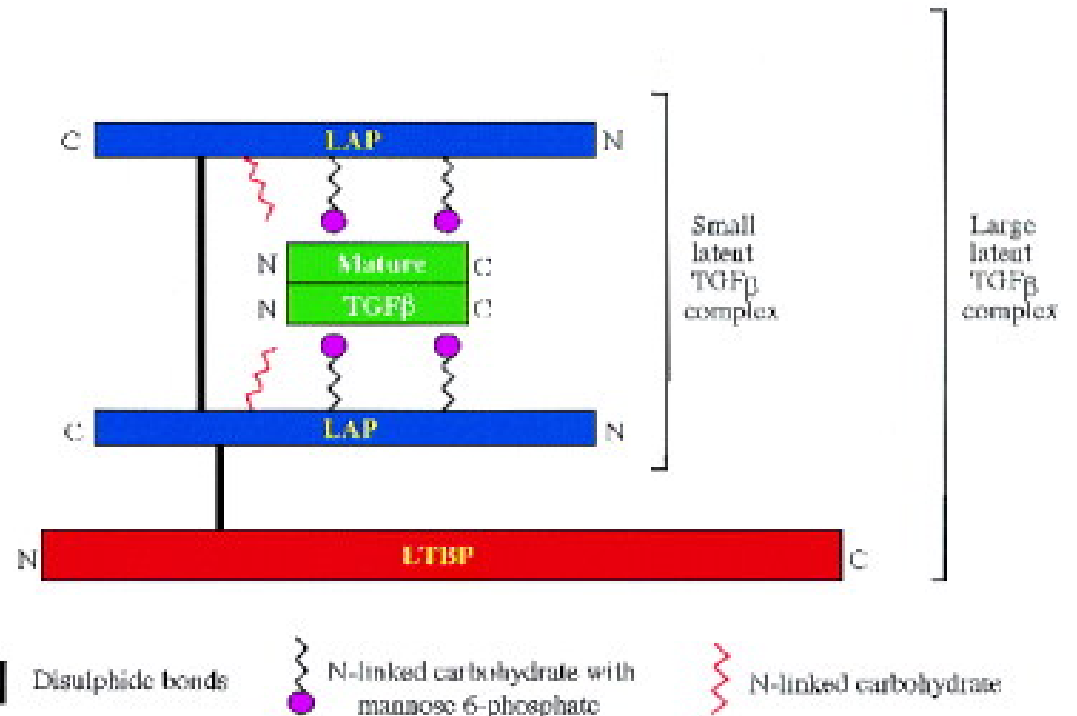
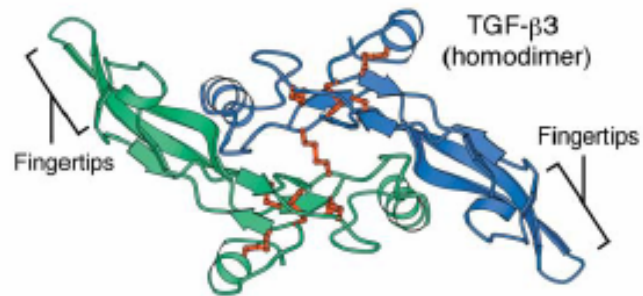
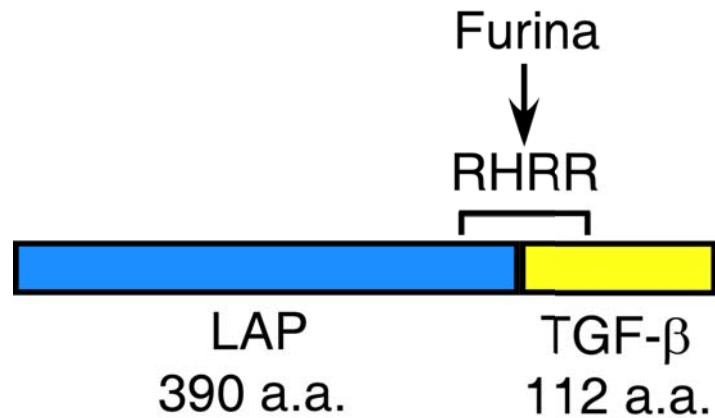


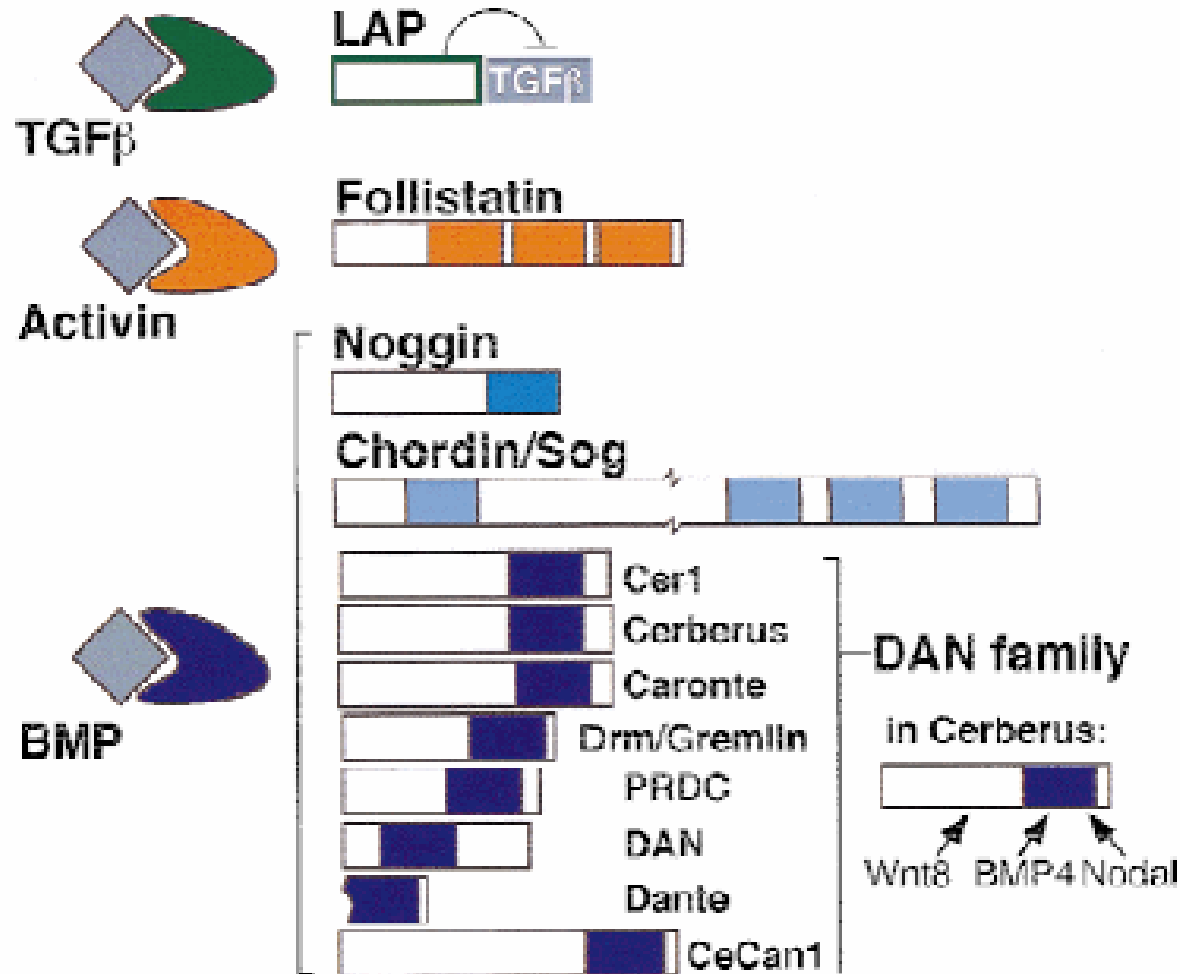
Figure 1. Effect of TGFs on the Proliferation and Morphology of Mv1Lu Cells.

Mv1Lu cells were seeded at a sparse (4×10^4 cells/cm²) density in medium containing 5% fetal calf serum alone (a) or with 0.3 nM TGFs (b). Cultures were photographed 4 days later. The normal size and morphology of control cells in sparse cultures was as can be seen in subconfluent areas of panel a.

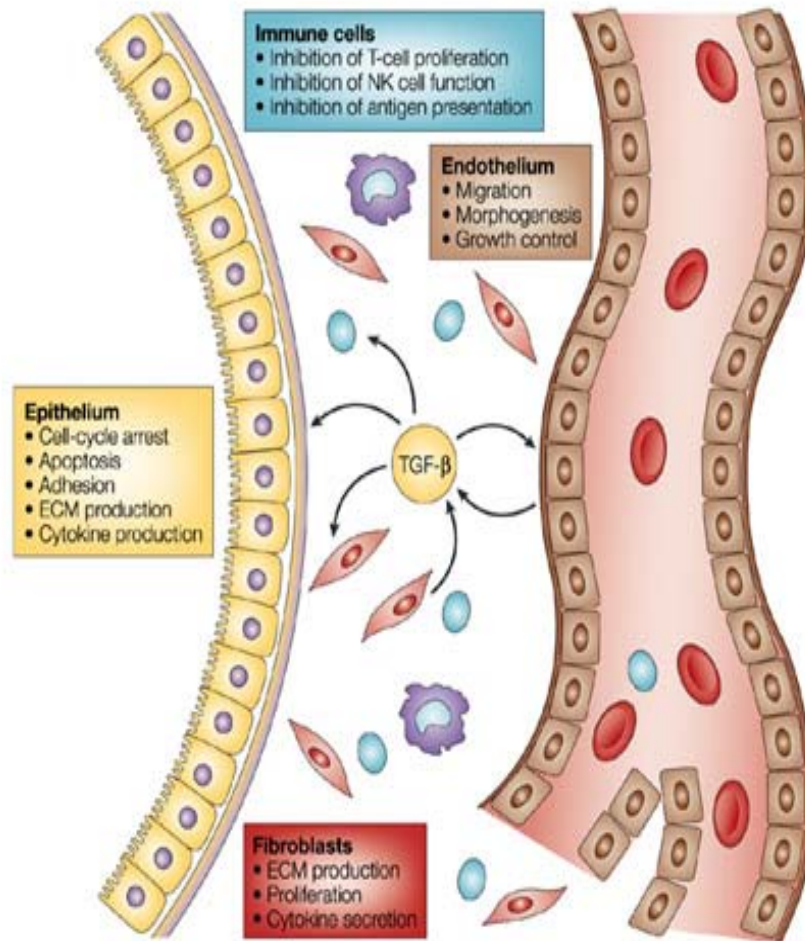
TGF- β Latente



Antagonistas o "atrapa ligandos" de la superfamilia del TGF- β



El Factor de Crecimiento Transformante- β (TGF- β)



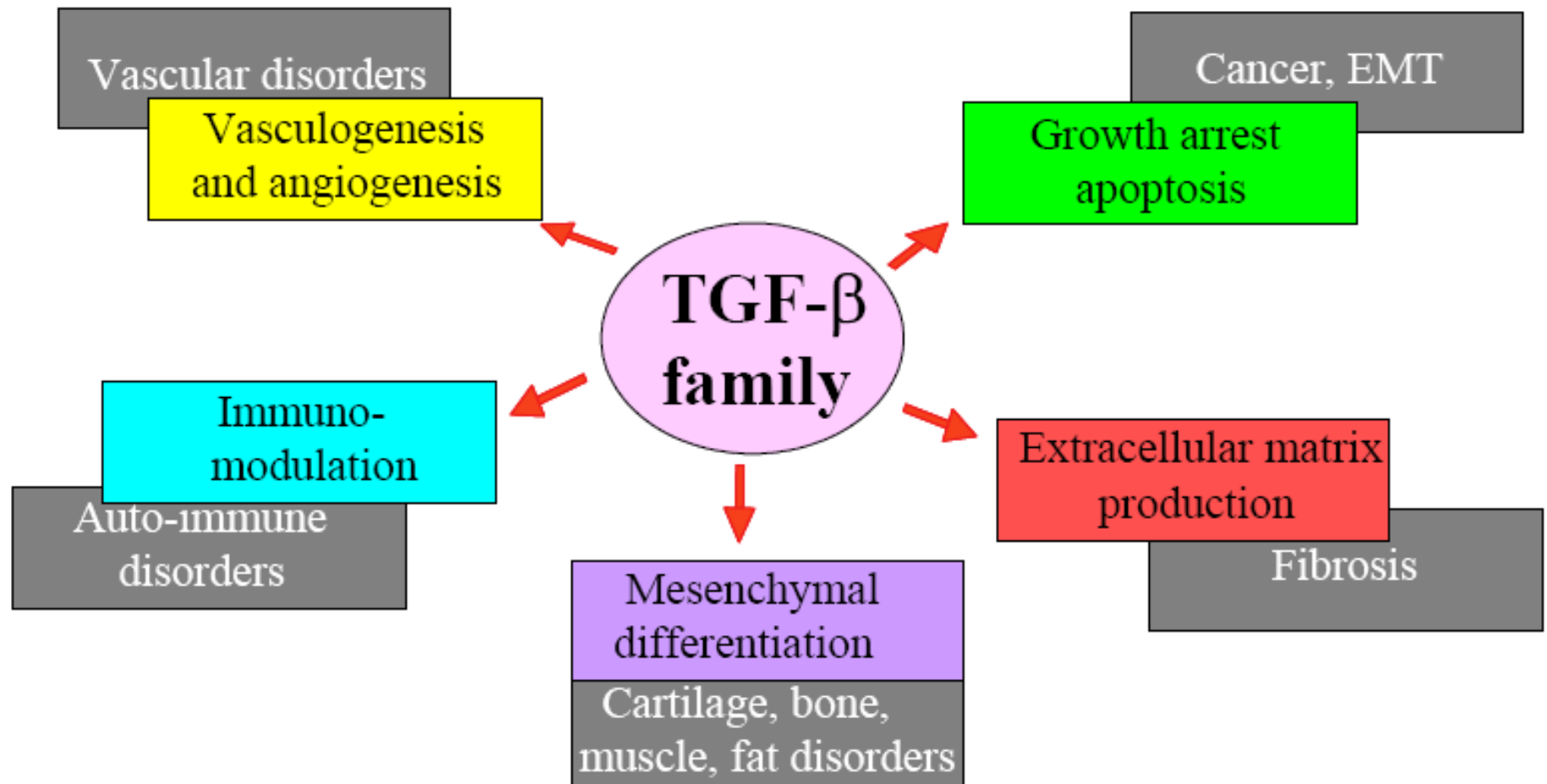
Nature Reviews | Cancer

Regula diversos procesos celulares:

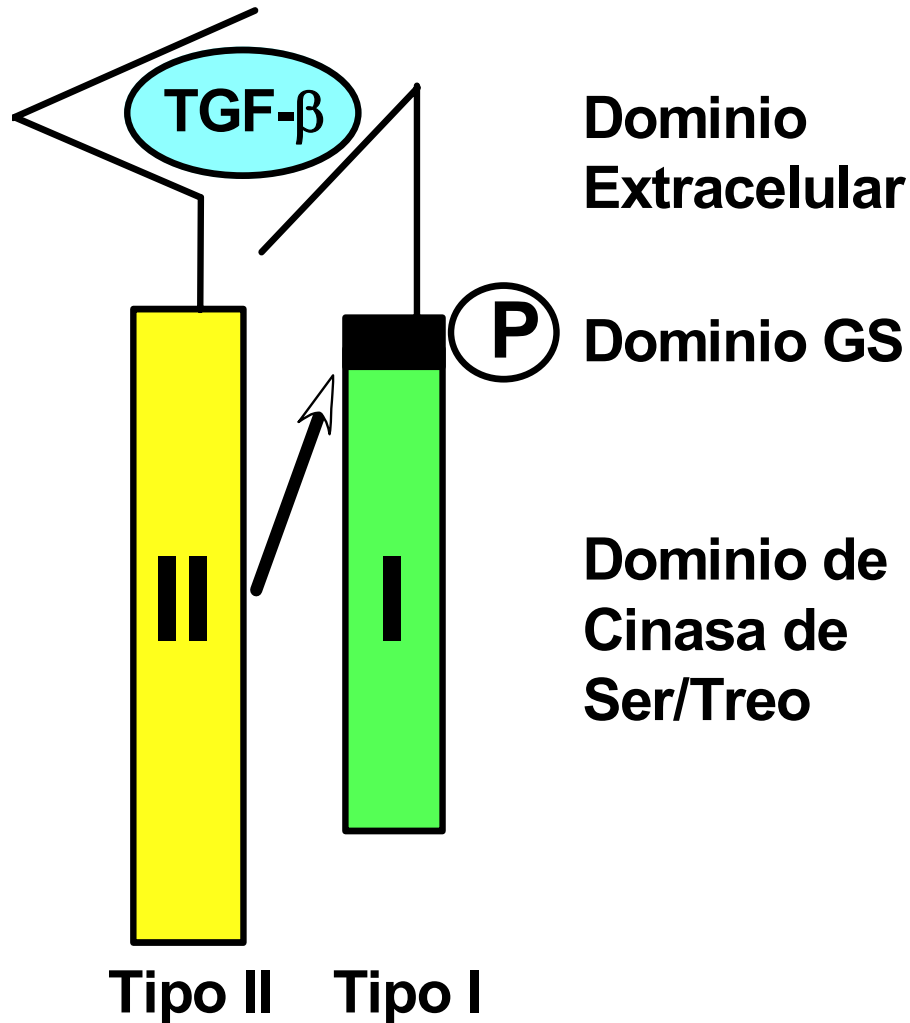
- Desarrollo embrionario
- Morfogénesis
- Crecimiento, diferenciación y muerte
- Homeostasis celular
- Reparación Tisular (fibrosis)
- Respuesta inmune
- Angiogénesis y vasculogénesis
- Cáncer

"Inhibe la Proliferación Celular"

FUNCIONES BIOLOGICAS DE LA FAMILIA DEL TGF- β



Receptores para la superfamilia del TGF- β



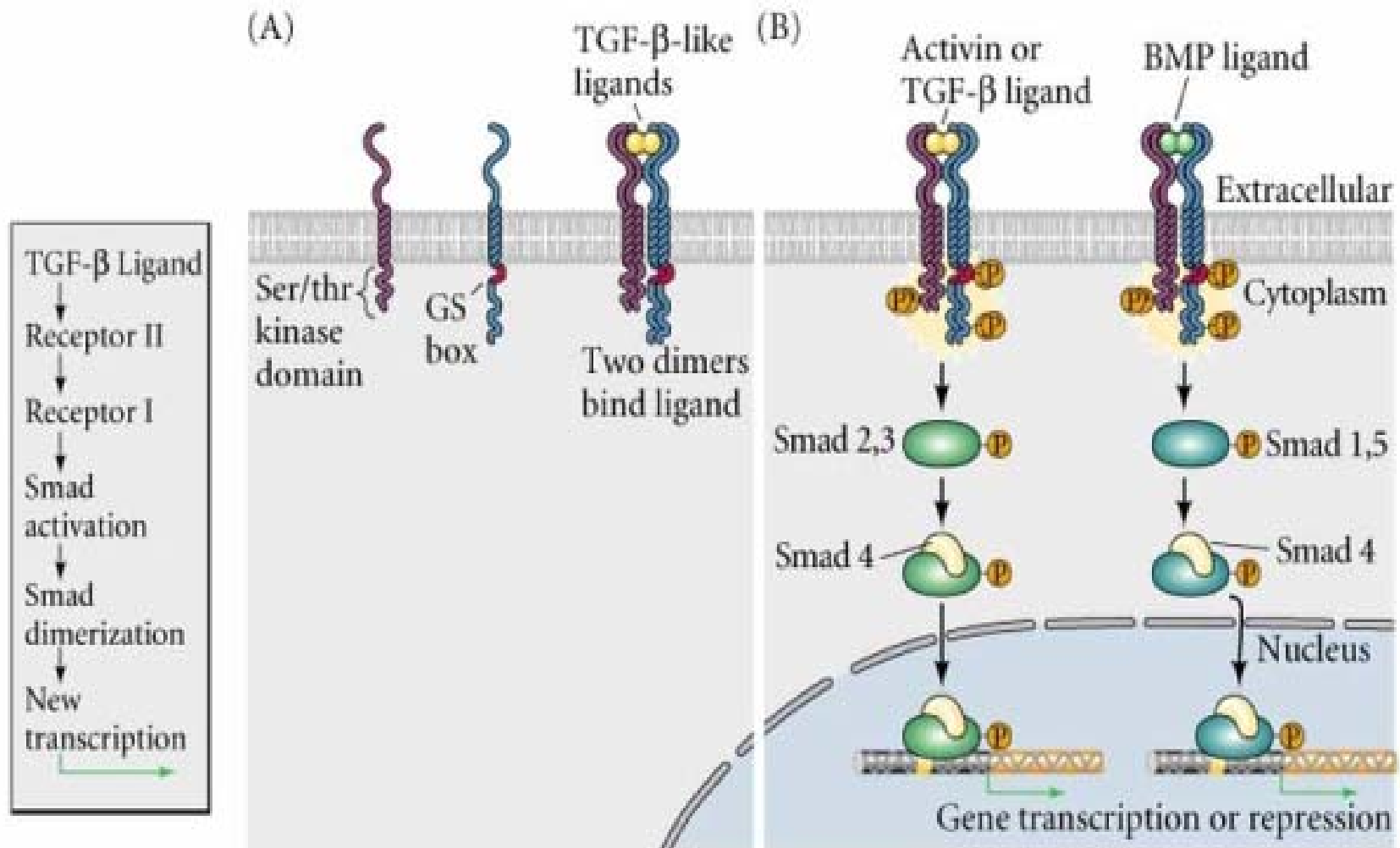
Receptores tipo II

T β RII
ActRII
ActRIIB
BMPRII
AMHR

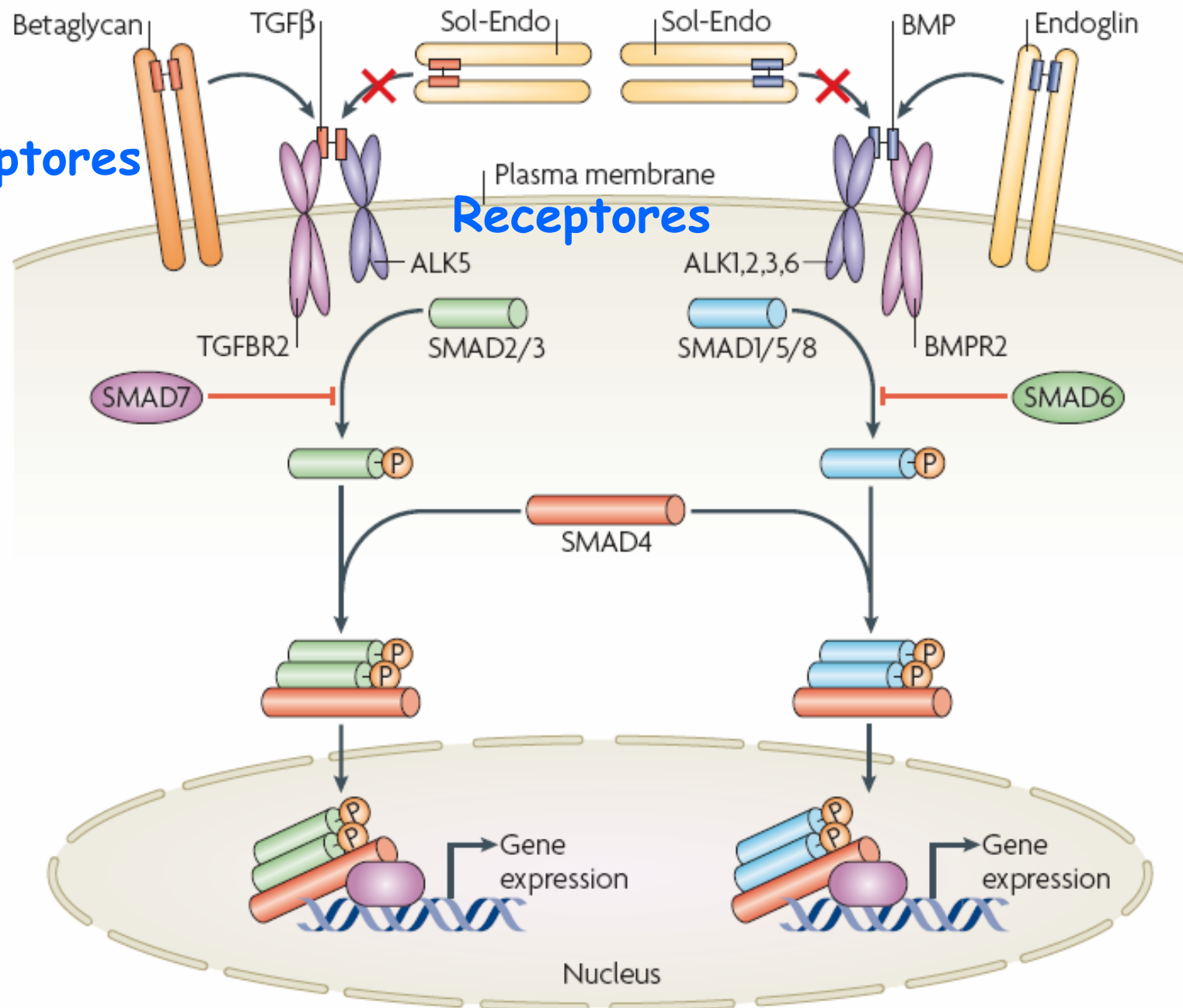
Receptores tipo I

ALK1/TSR1
ALK2/ActRI
ALK3/BMPRIA
ALK4/ActRIIB
ALK5/T β RI
ALK6/BMPRIIB
ALK7

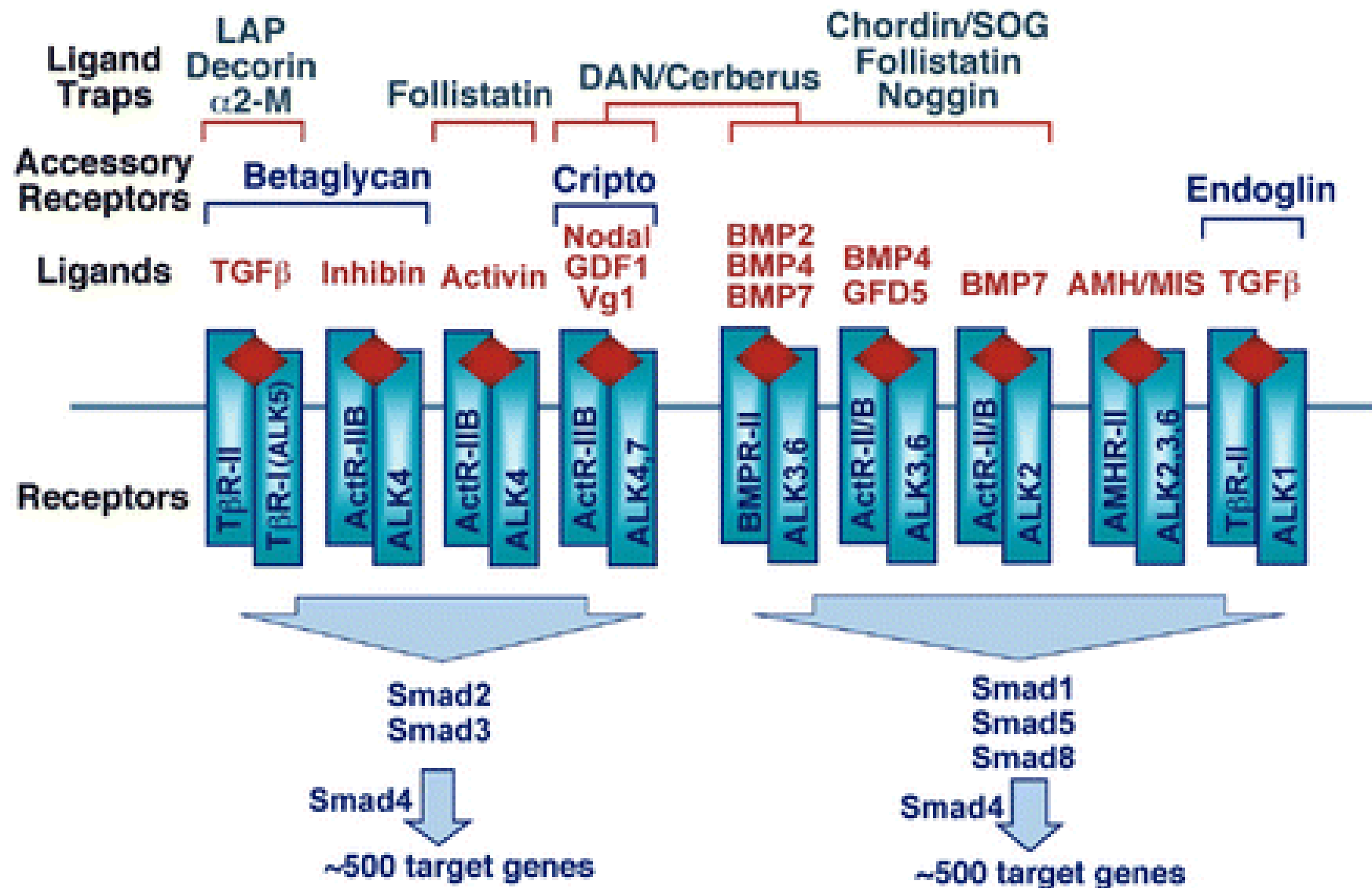
Sistema de Transducción del TGF- β



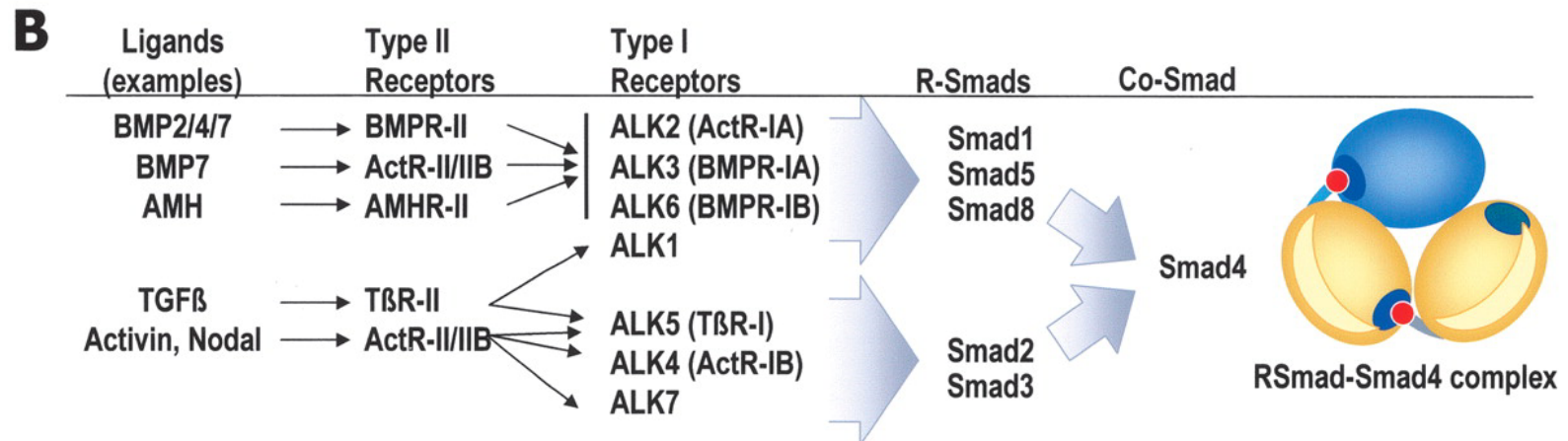
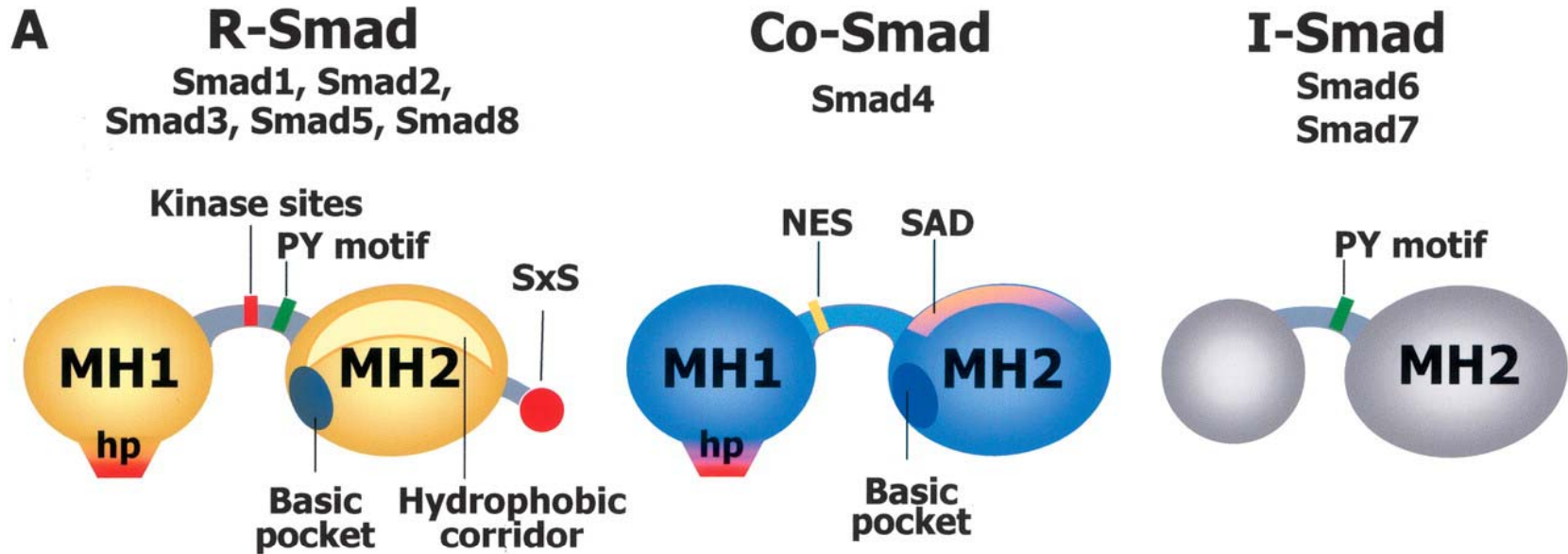
Co-Receptores



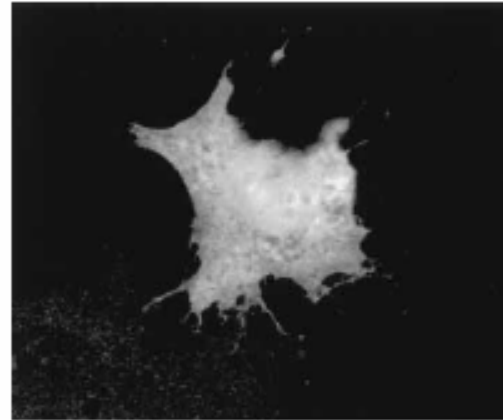
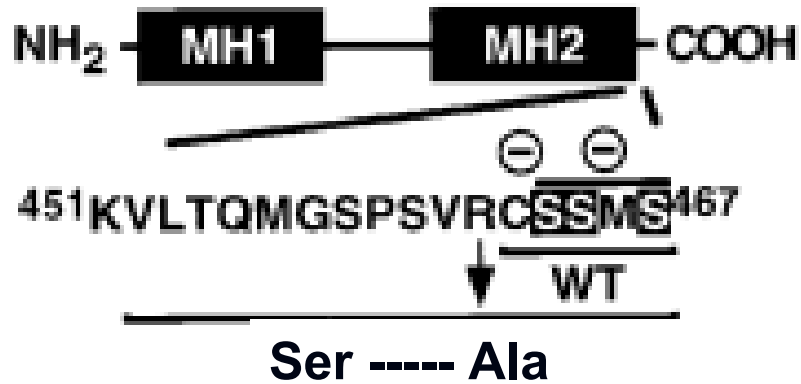
Sistema de Transducción del TGF- β



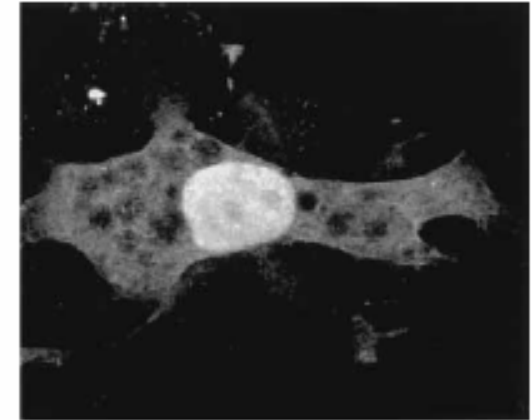
LAS SMAD SON FACTORES DE TRANSCRIPCION



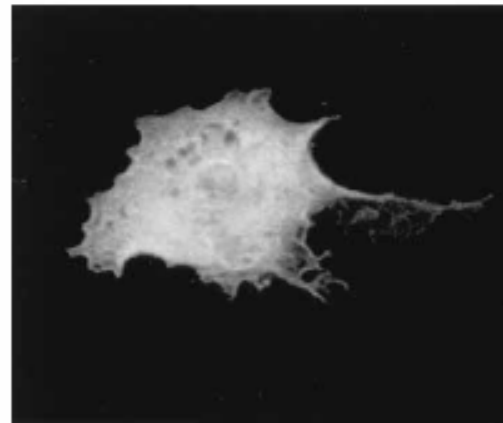
Activación de las Smads por el TGF- β



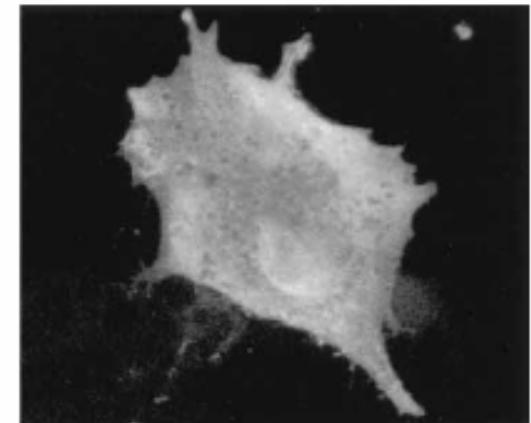
Smad2



Smad2 + T β RI*



Smad2 (3S-A)

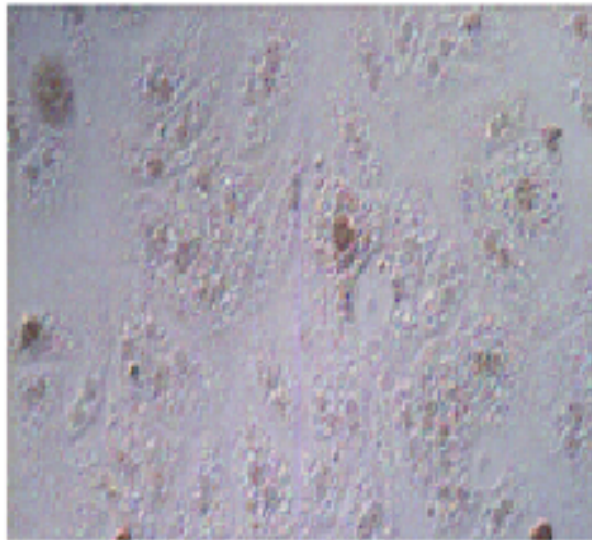


Smad2 (3S-A) + T β RI*

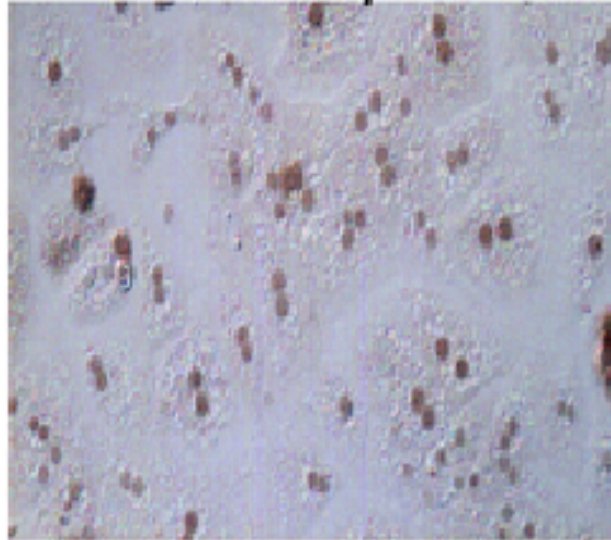
Activación de las Smads por el TGF- β en hepatocitos

A. Smad2/3 in hepatocytes nuclei.

CONTROL

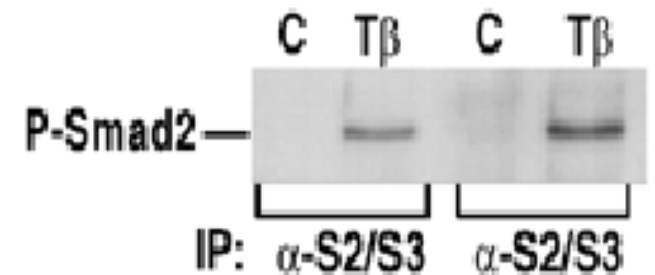


TGF- β

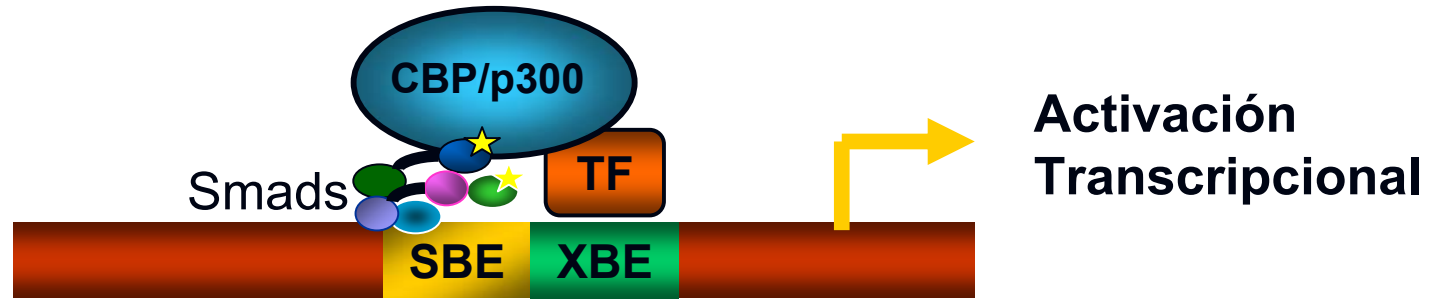


B. Western blot.

Cultured hepatocytes



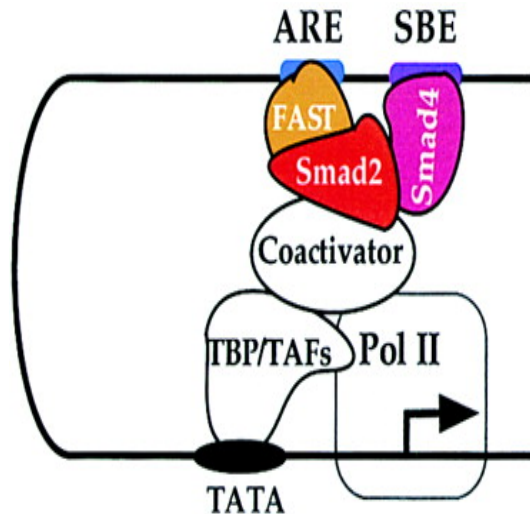
LAS SMAD SON FACTORES DE TRANSCRIPCION



Promotor de Genes Blanco

SBE: Elemento de Unión de Smads

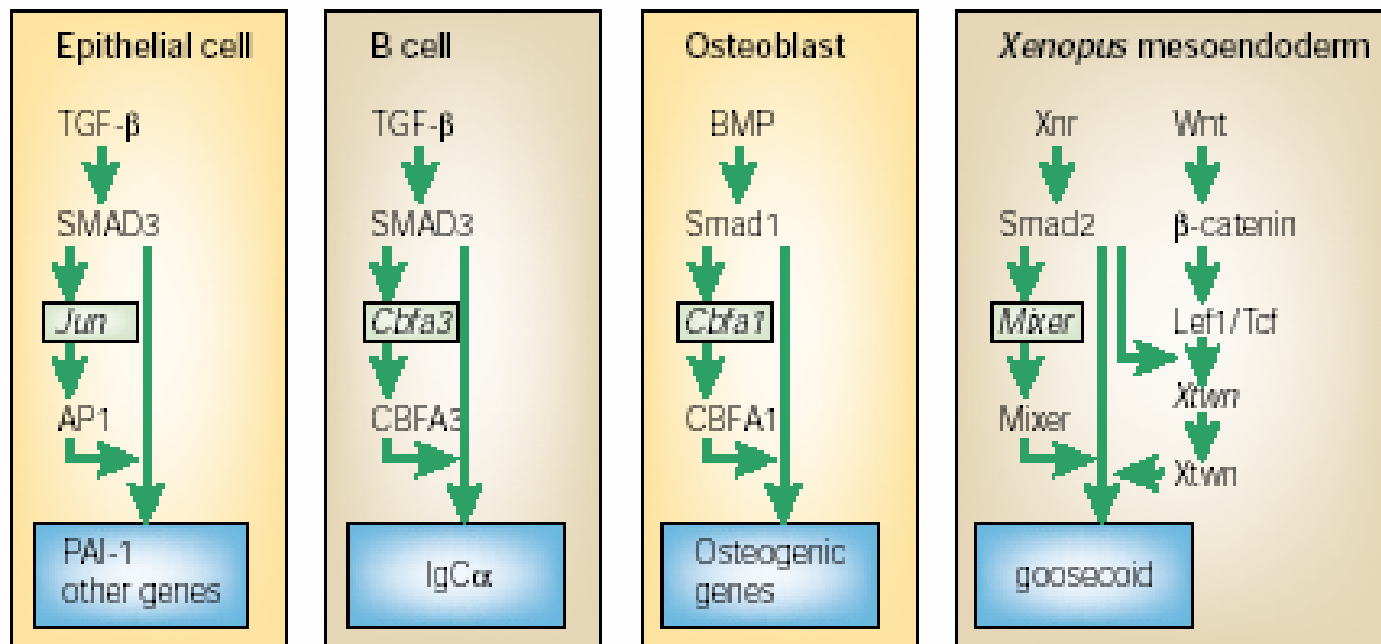
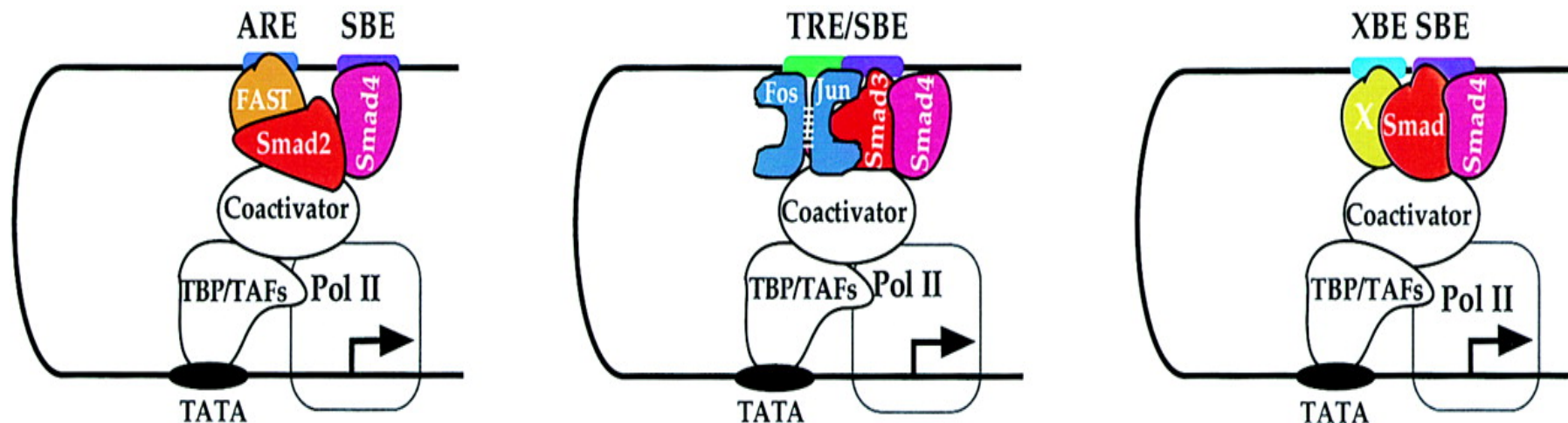
XBE: Elemento de Unión de Factores de Transcripción Específicos



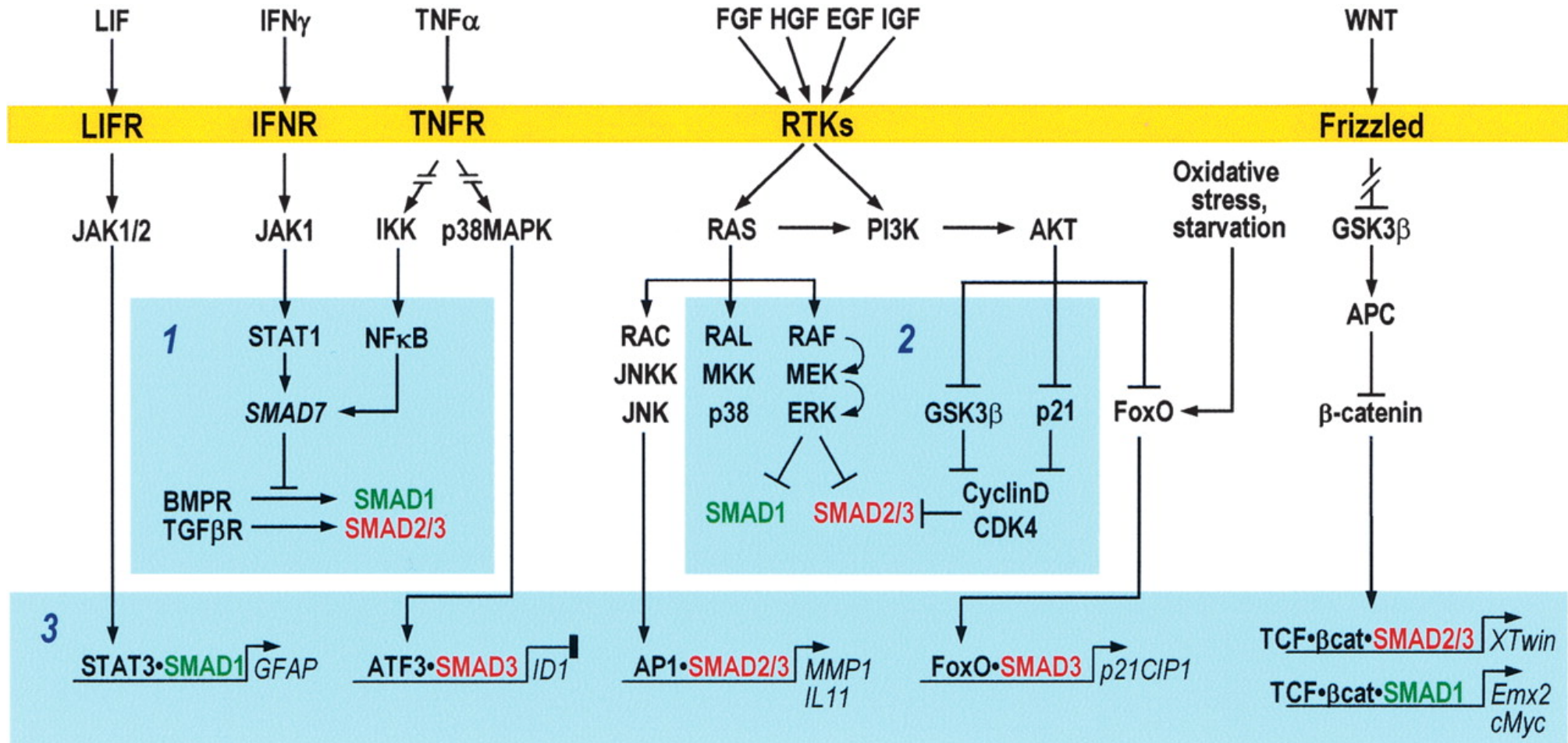
Smad Binding Element
(SBEs):
CAGACA

Mix2

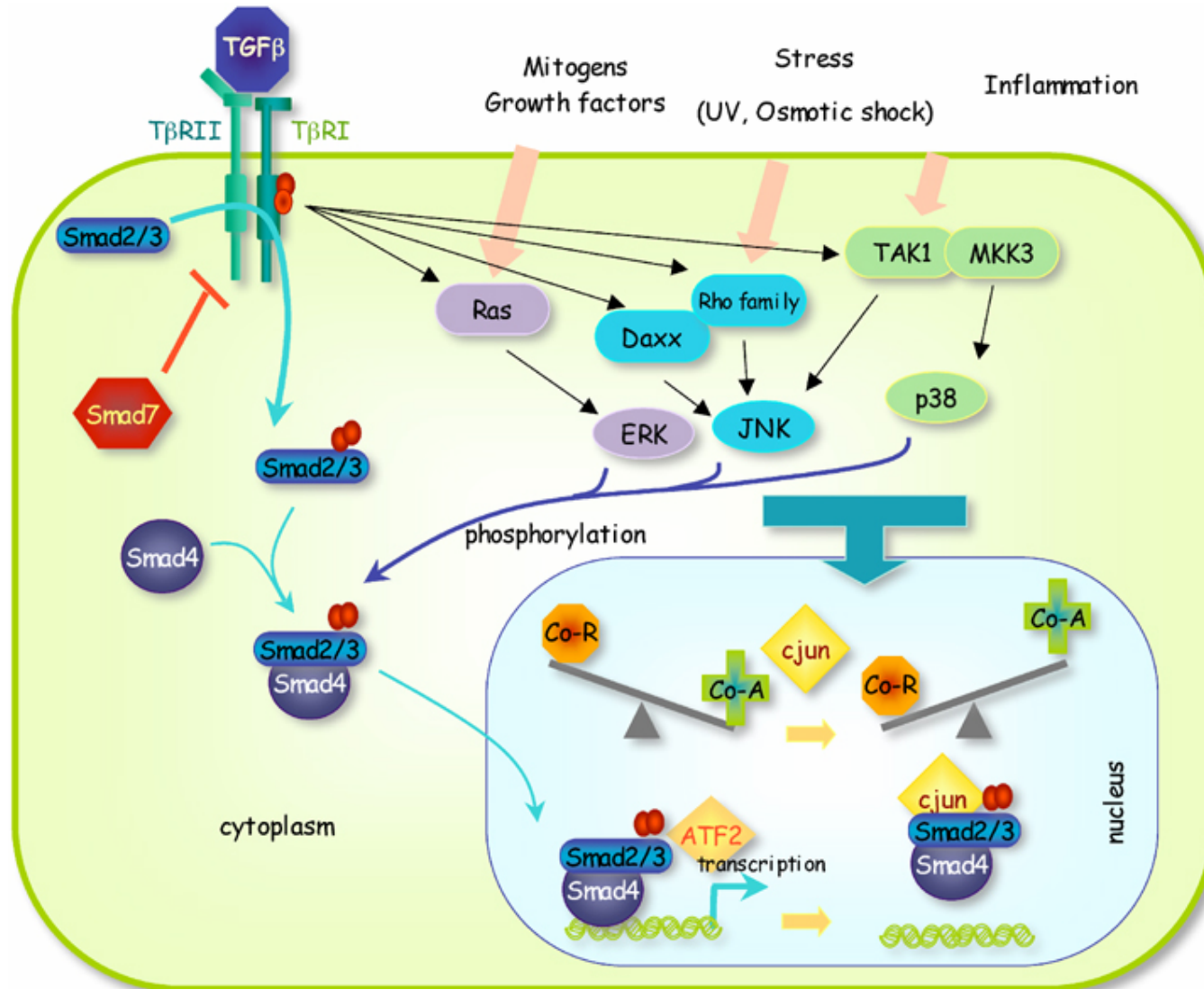
Las Smads son Factores de Transcripción



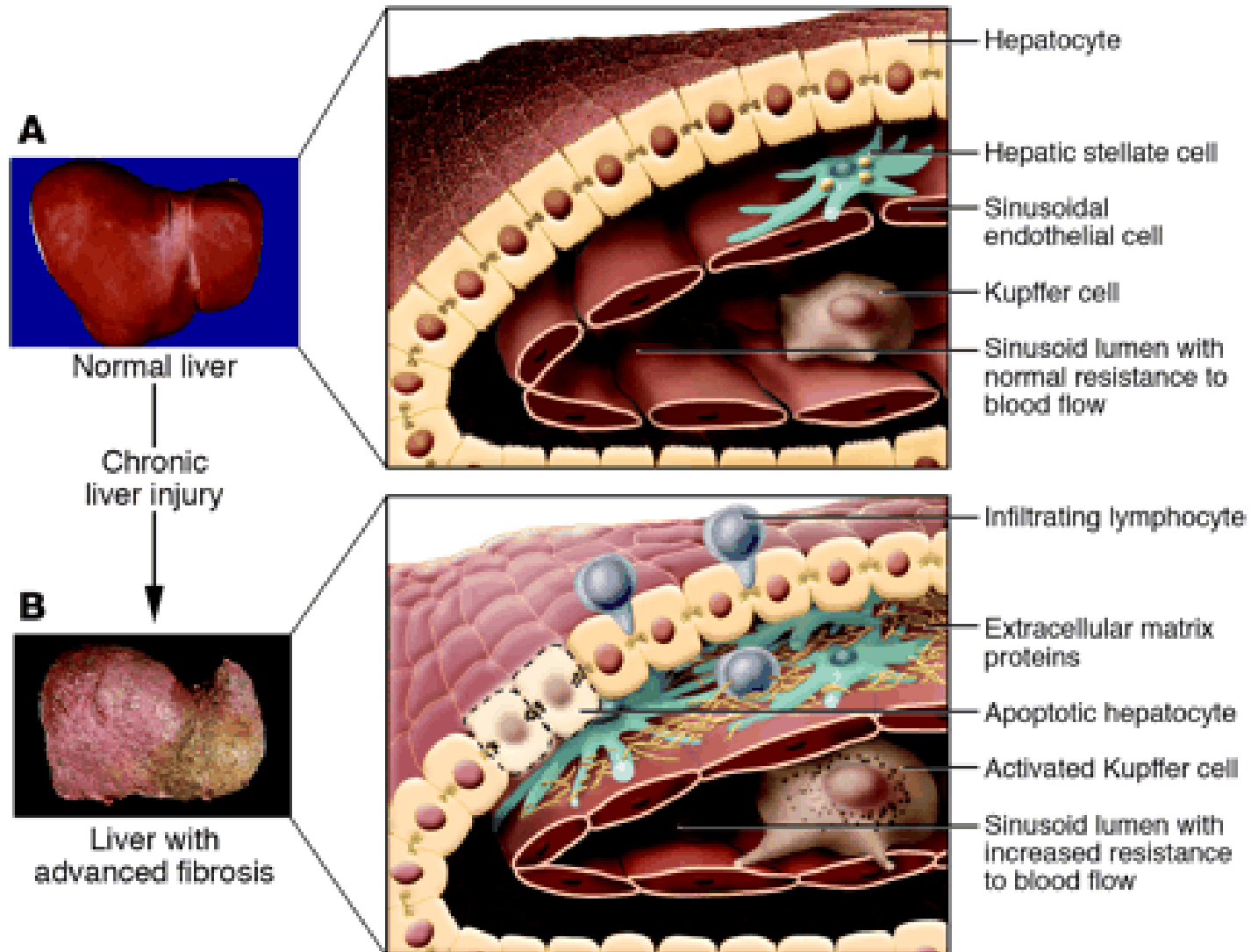
Regulación Transcripcional por el TGF- β



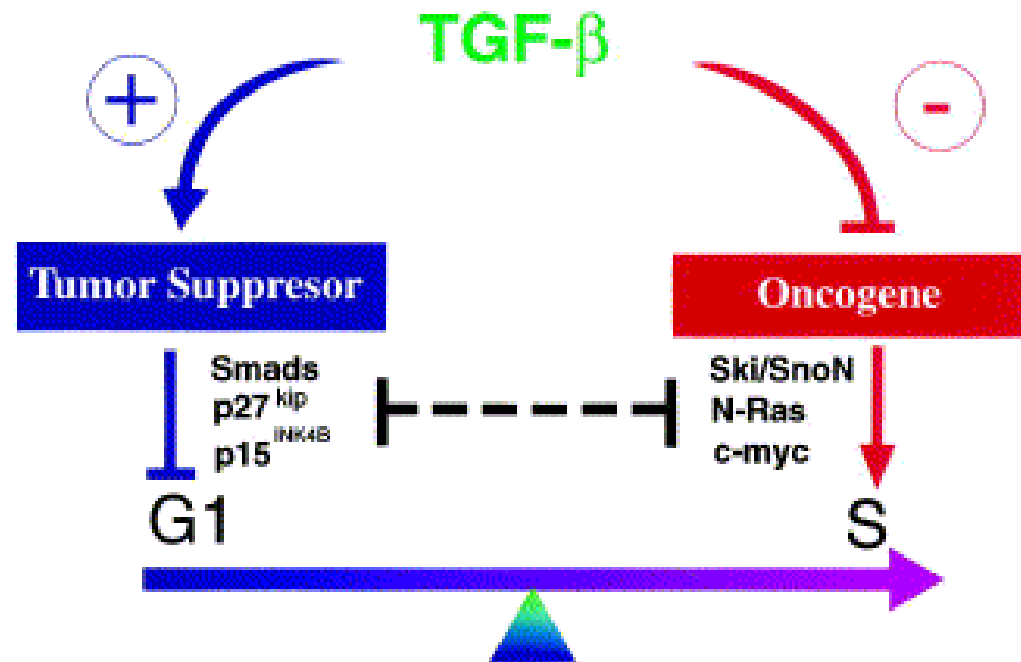
El TGF- β activa vías de transducción alternas



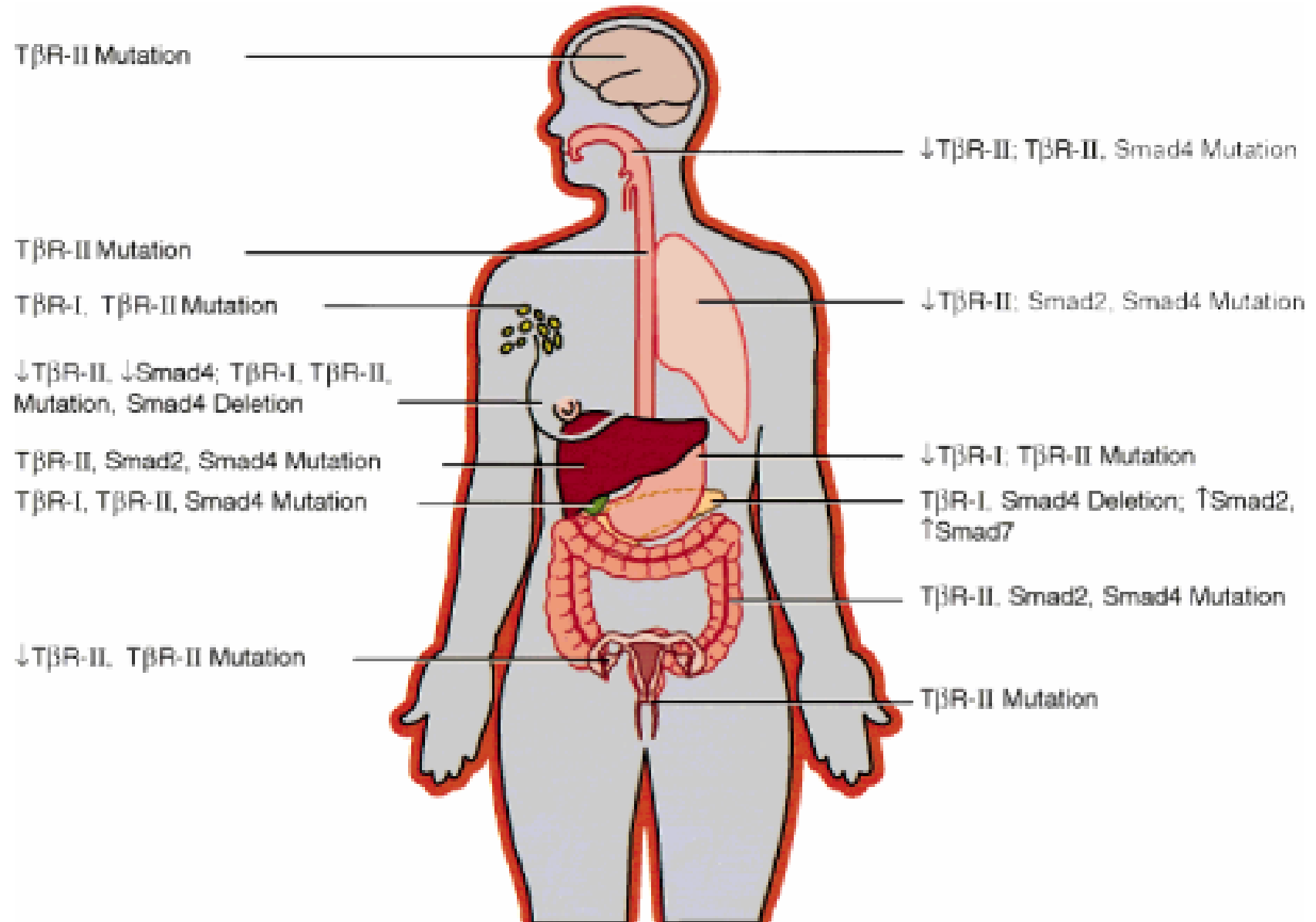
El TGF- β favorece la Fibrosis



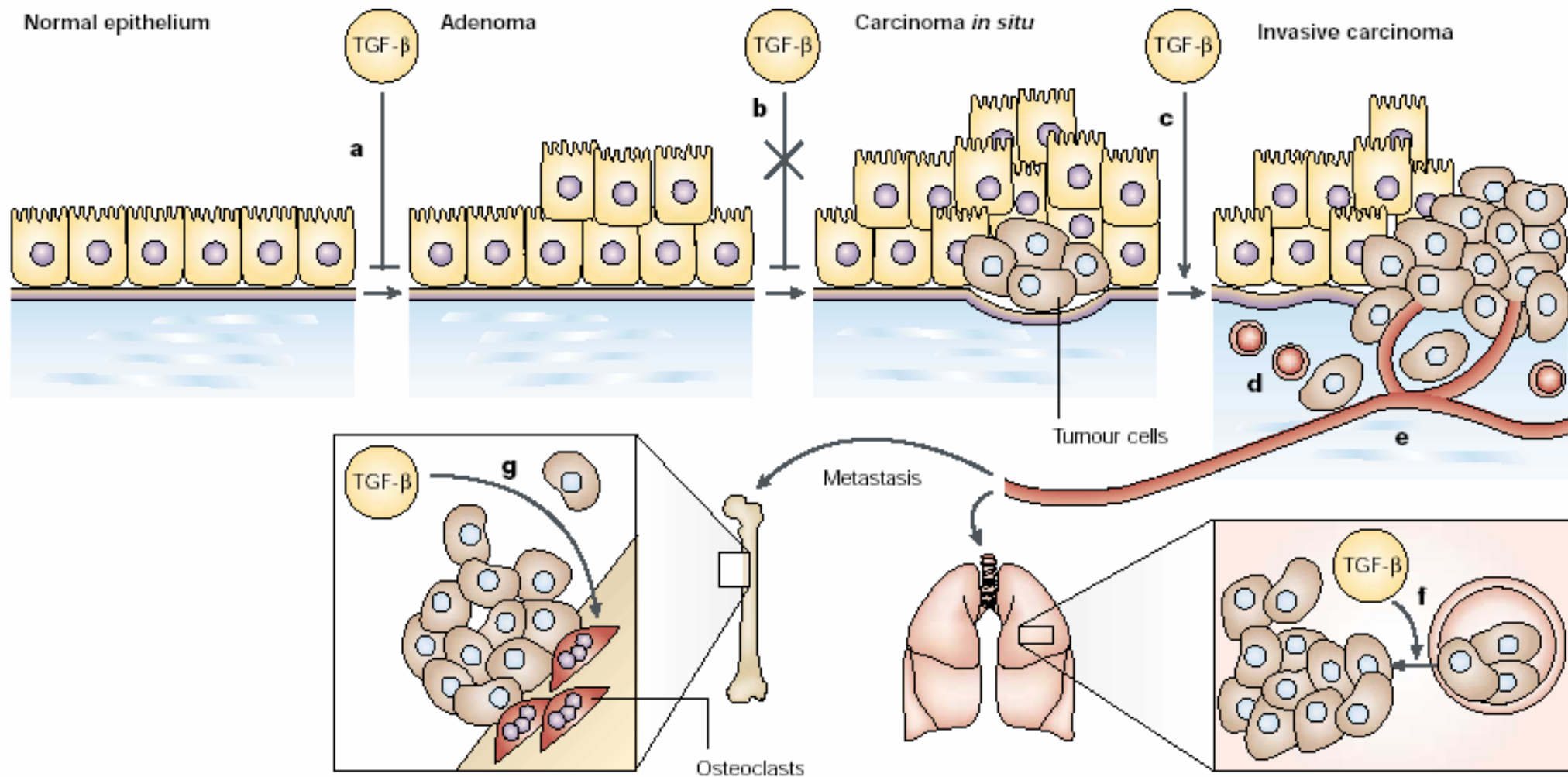
El TGF- β inhibe la proliferación celular



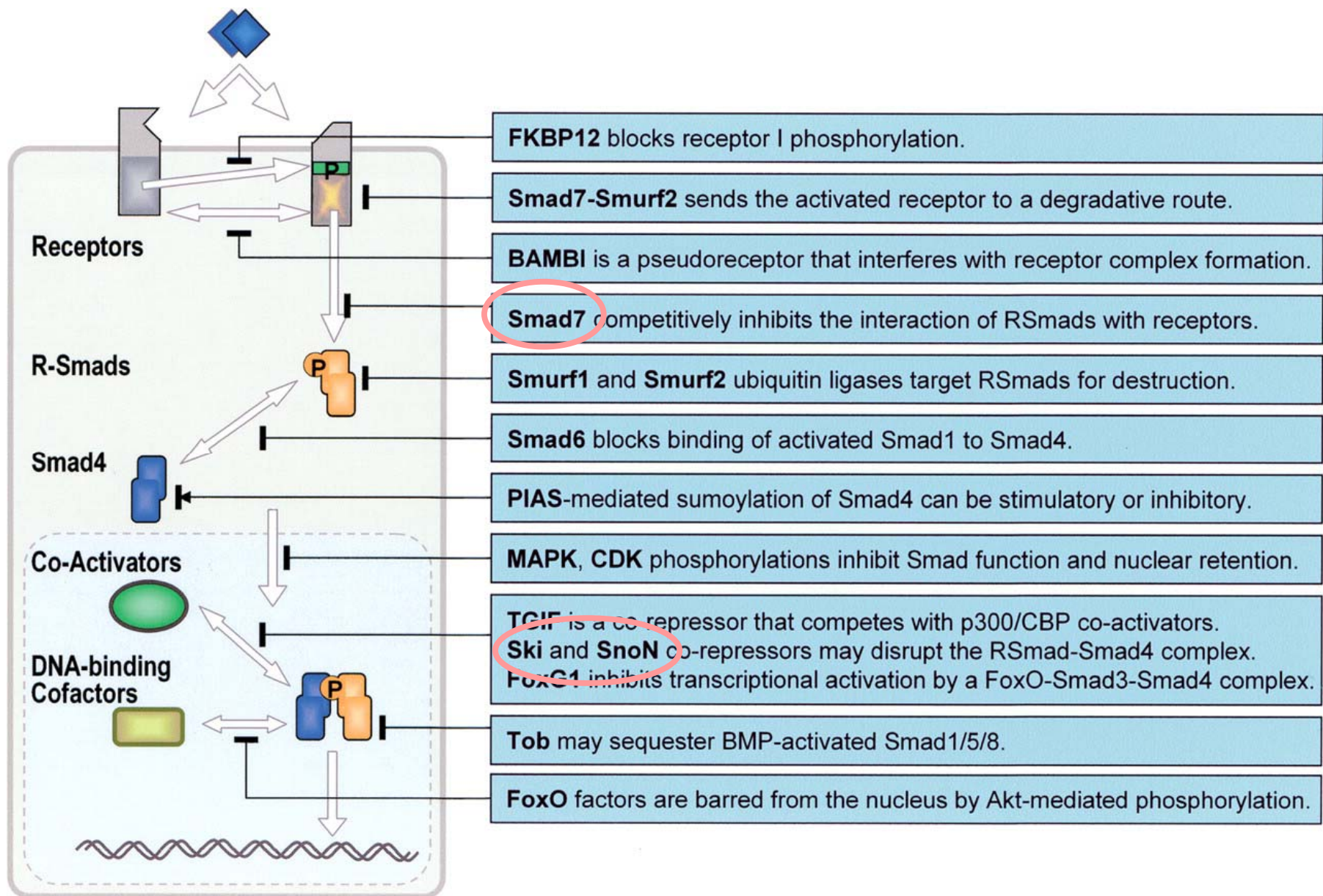
El TGF- β y su papel en el cáncer



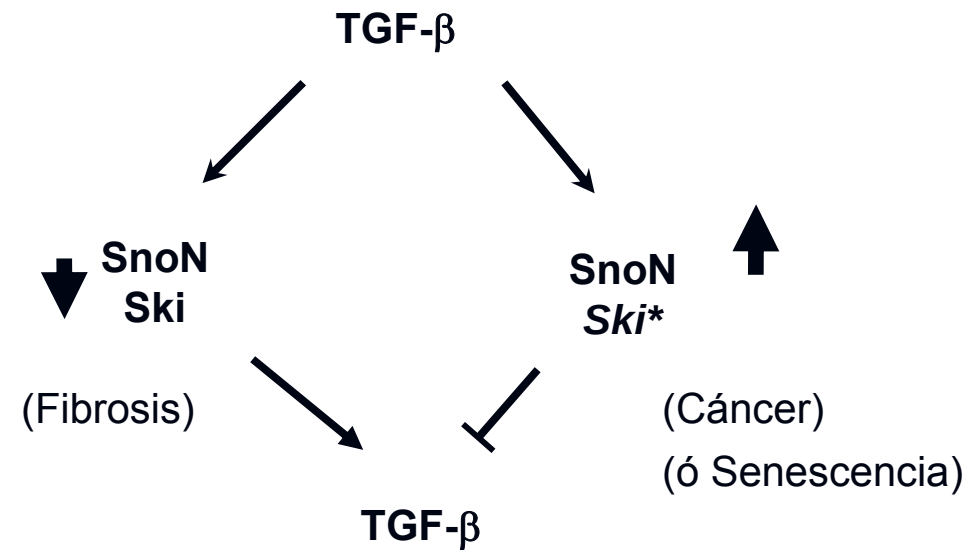
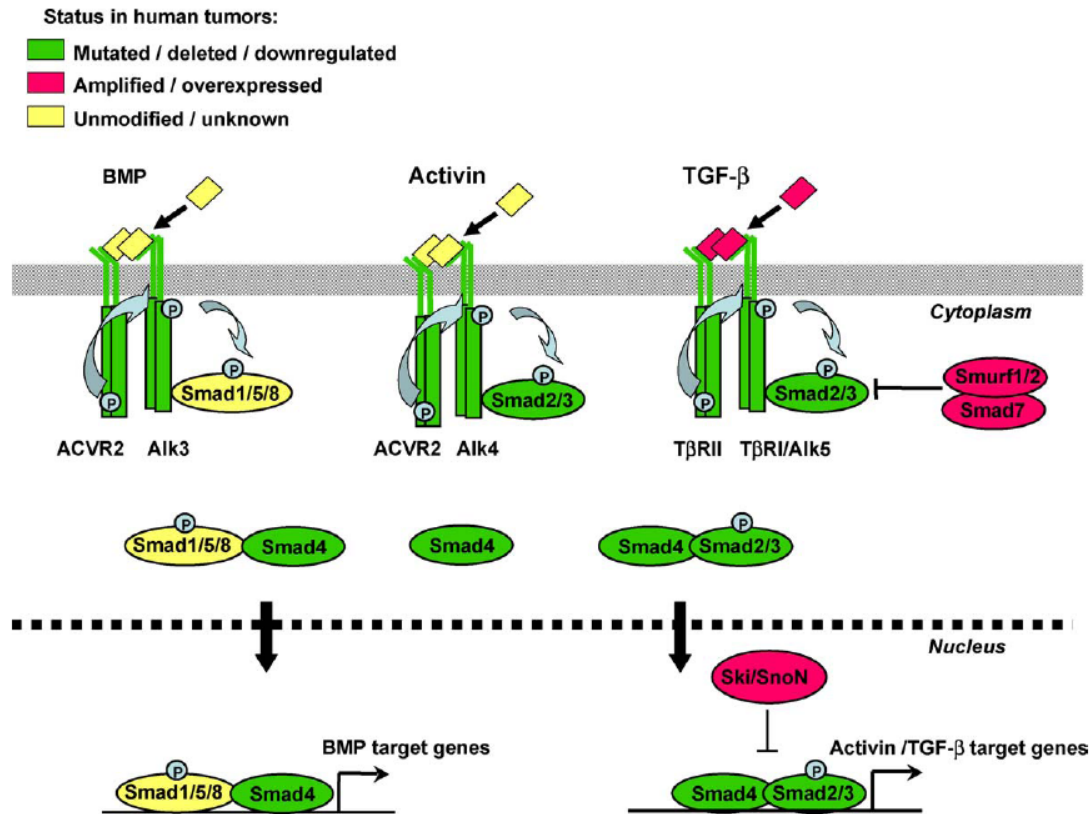
El TGF- β y su papel en el cáncer



Regulación de la Vía del TGF- β



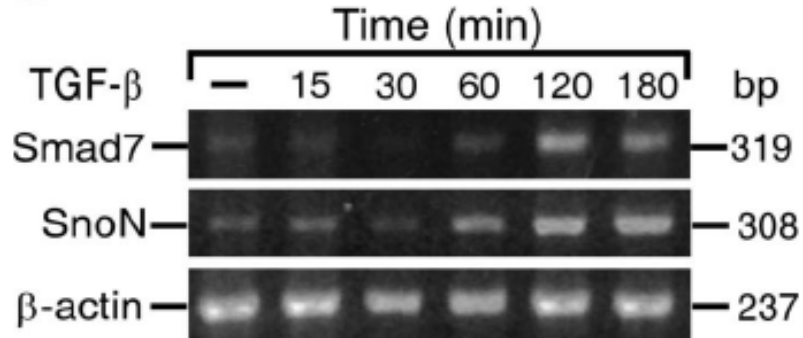
Regulación de los niveles de Smad7, Ski y SnoN regulan la vía del TGF- β



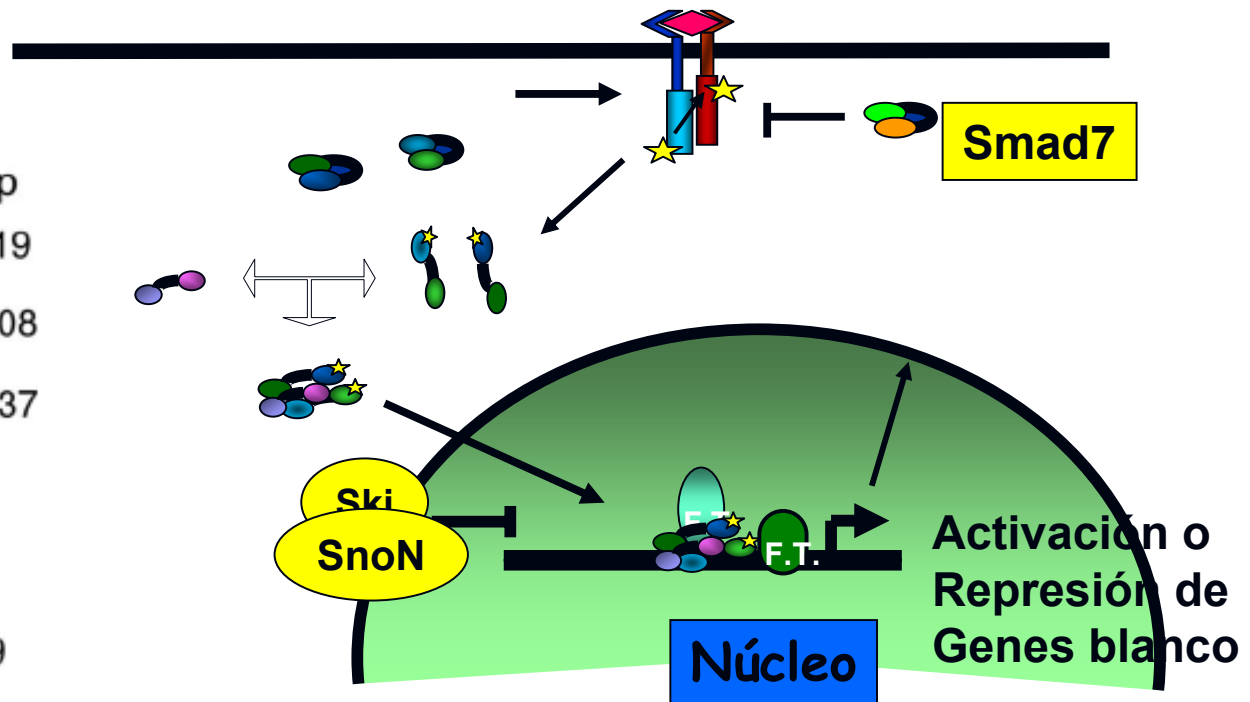
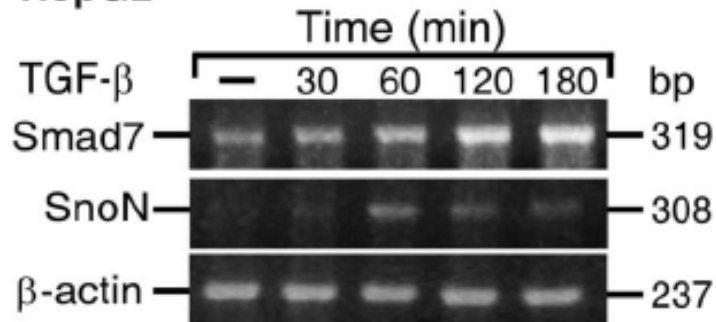
Regulación de los genes *smad7* y *sno* por TGF- β .

Papel de las proteínas Smad7, Ski y SnoN en las asas de retroalimentación negativa de la vía

A A549



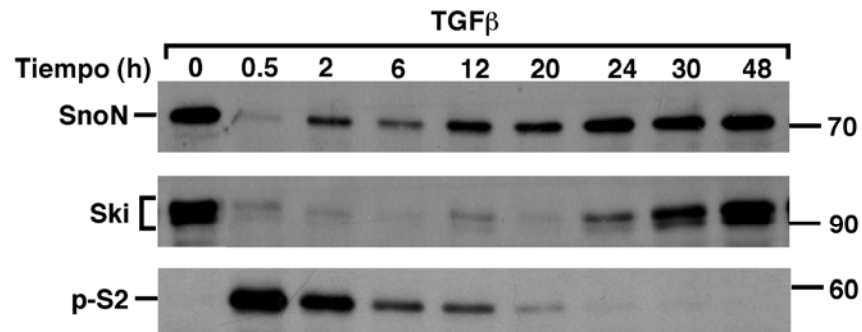
B HepG2



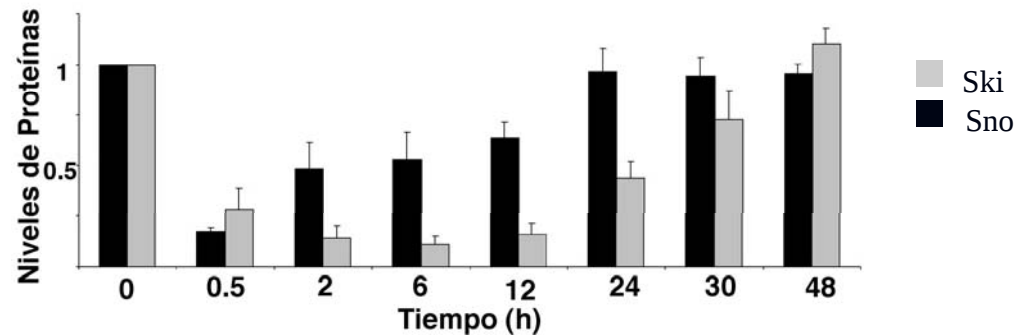
Regulación de Ski y SnoN por el TGF- β

HepG2

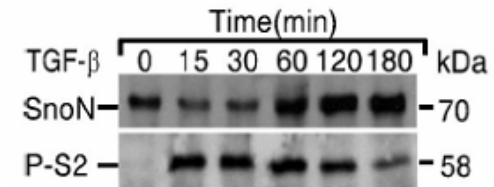
A



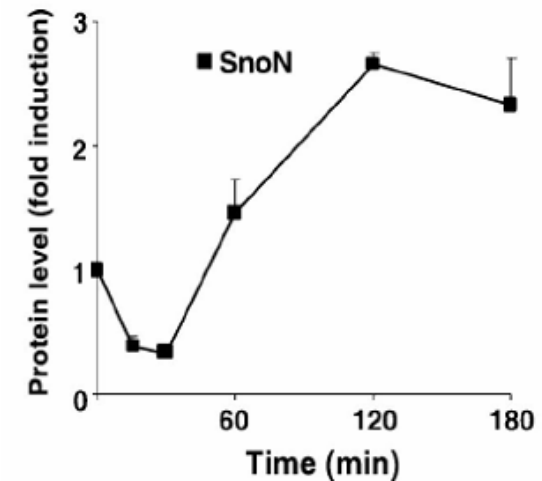
B



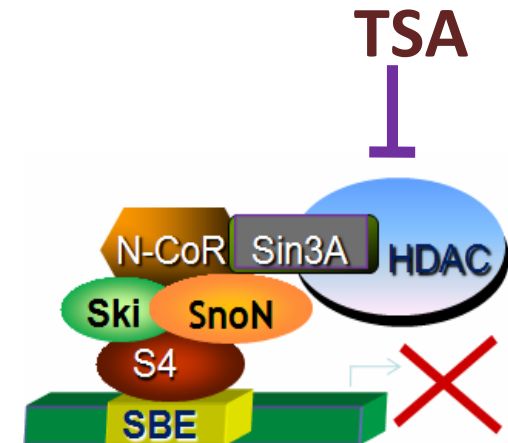
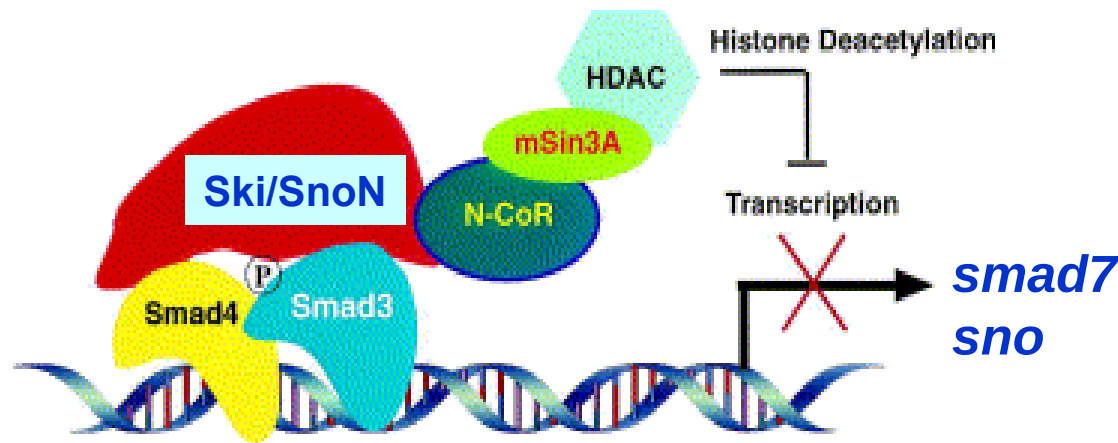
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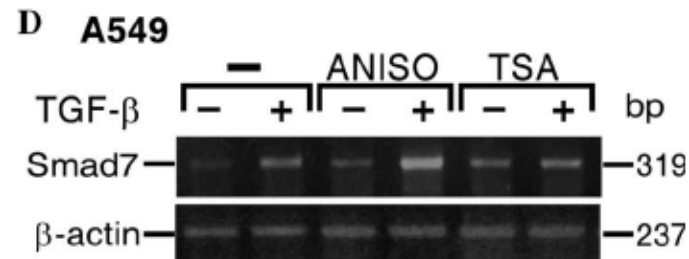
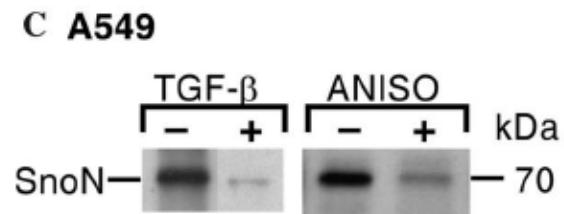
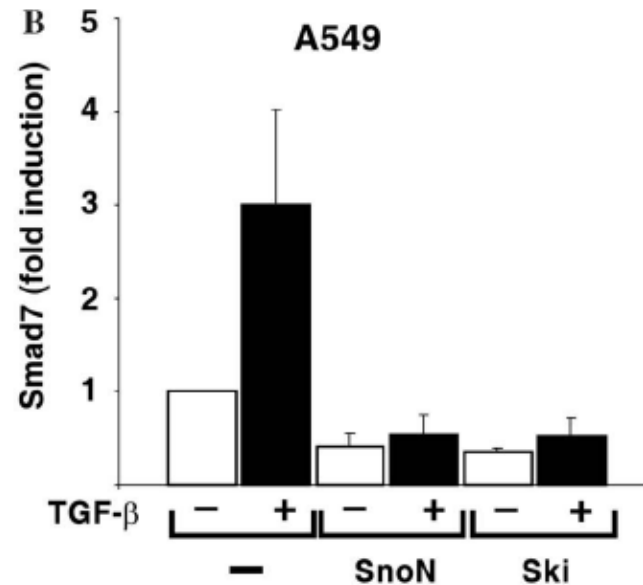
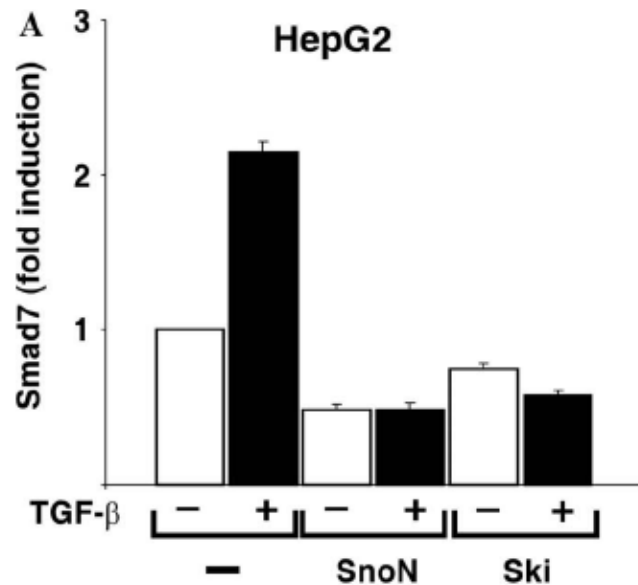
B A549



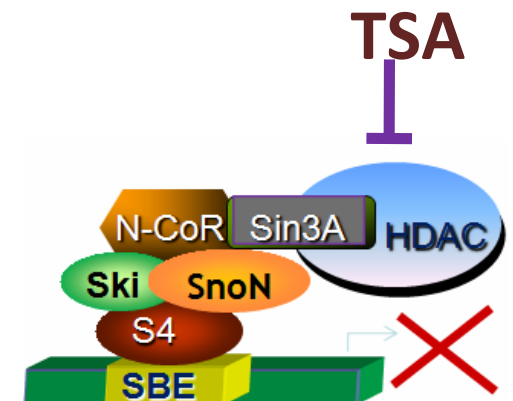
Mecanismo de Inhibición de la Actividad Transcripcional de las Smads por Ski/SnoN



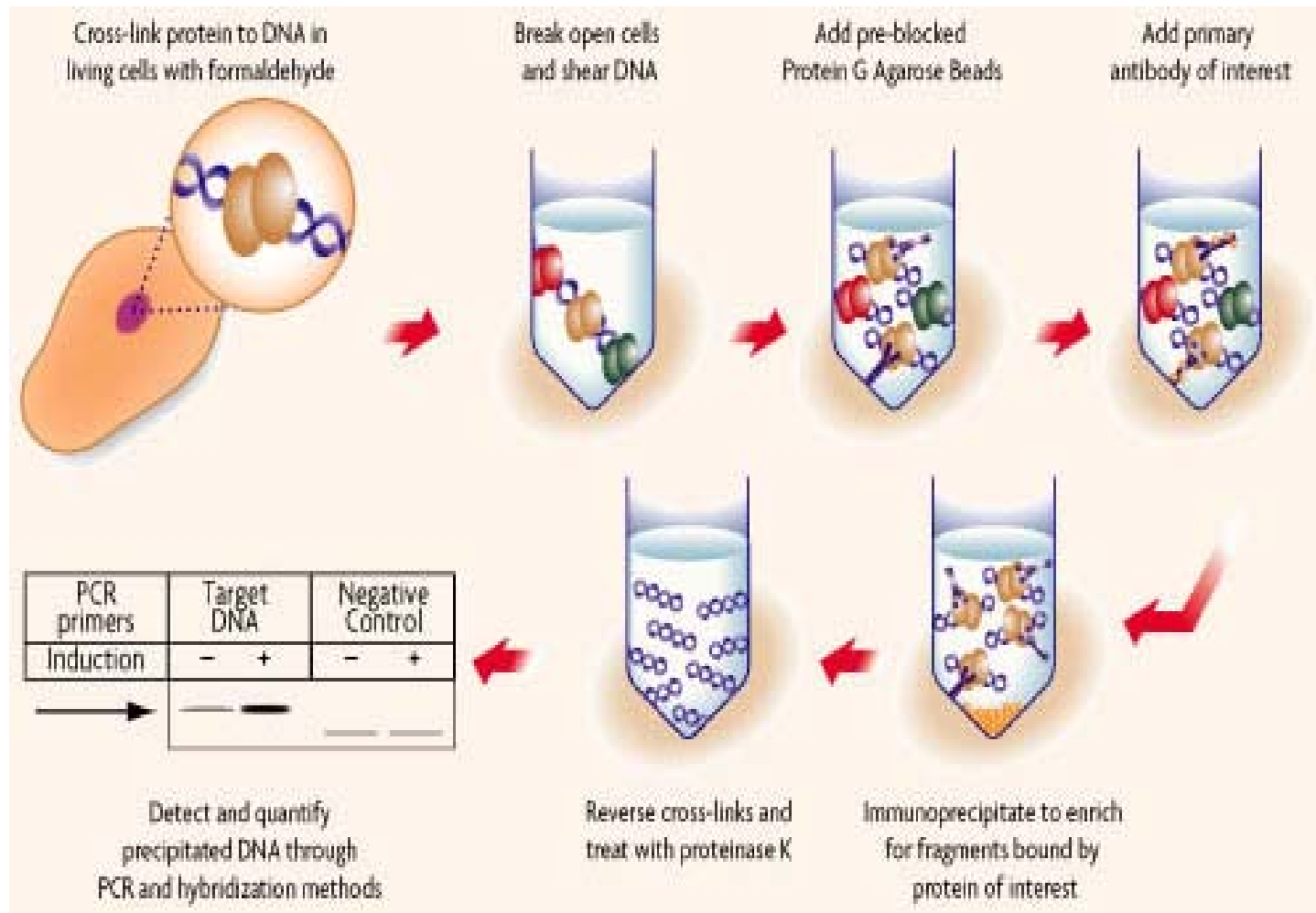
Regulación de Smad7 por Ski y SnoN



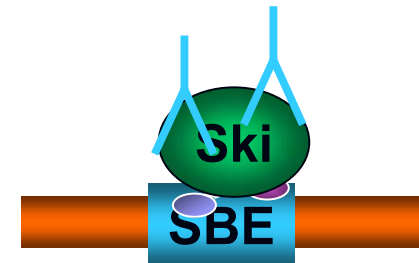
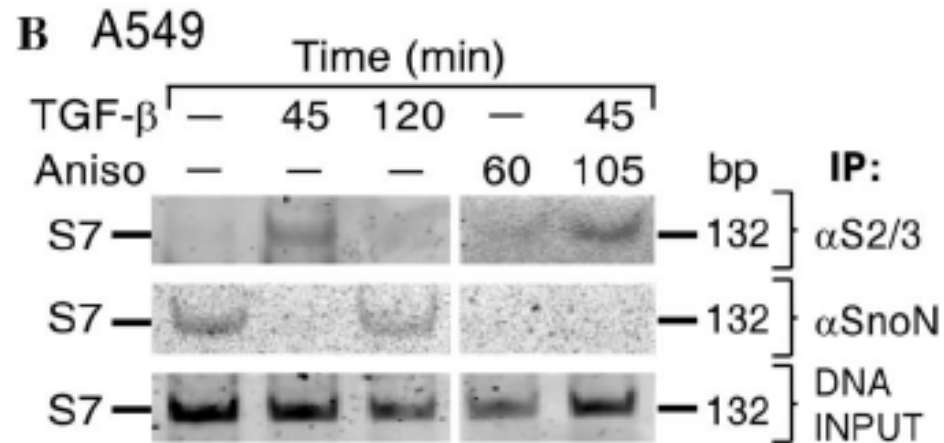
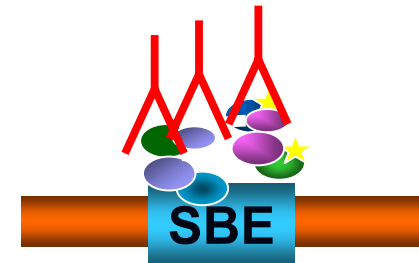
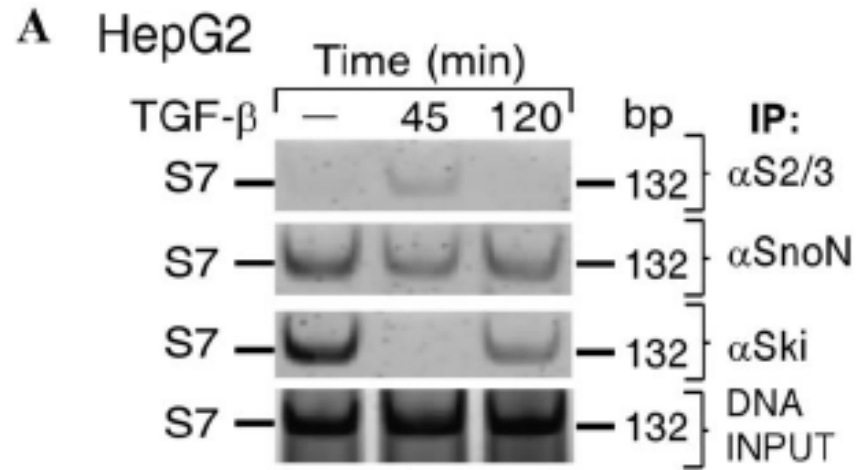
smad7SBEs-Luc



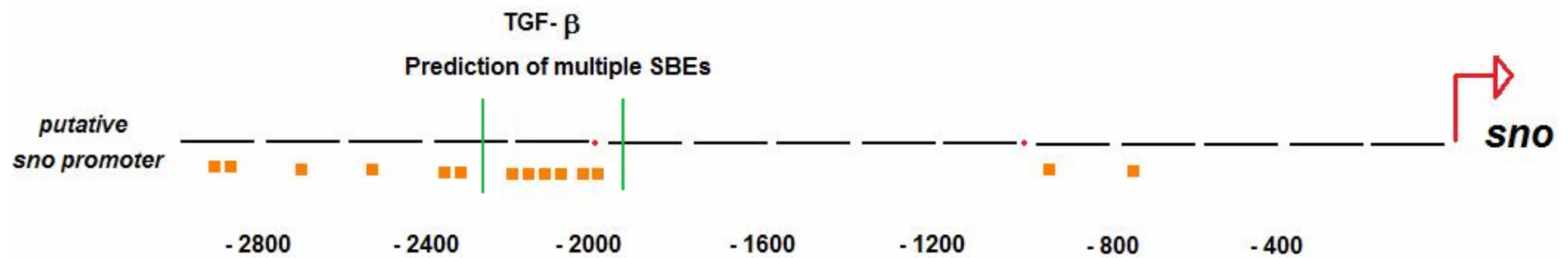
Inmunoprecipitación de cromatina



Regulación de Smad7 por Ski y SnoN



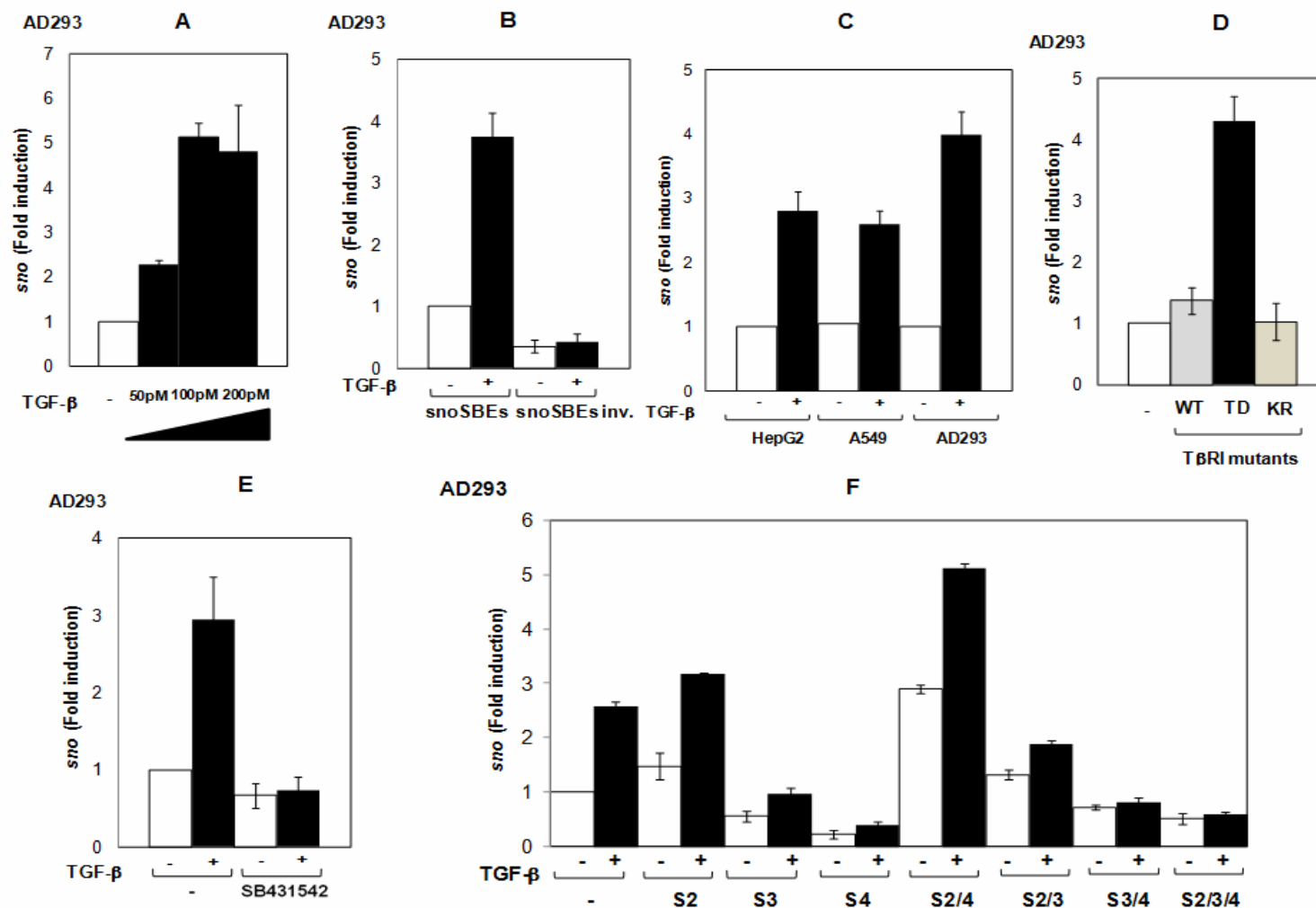
Regulación del gen *sno* por TGF- β



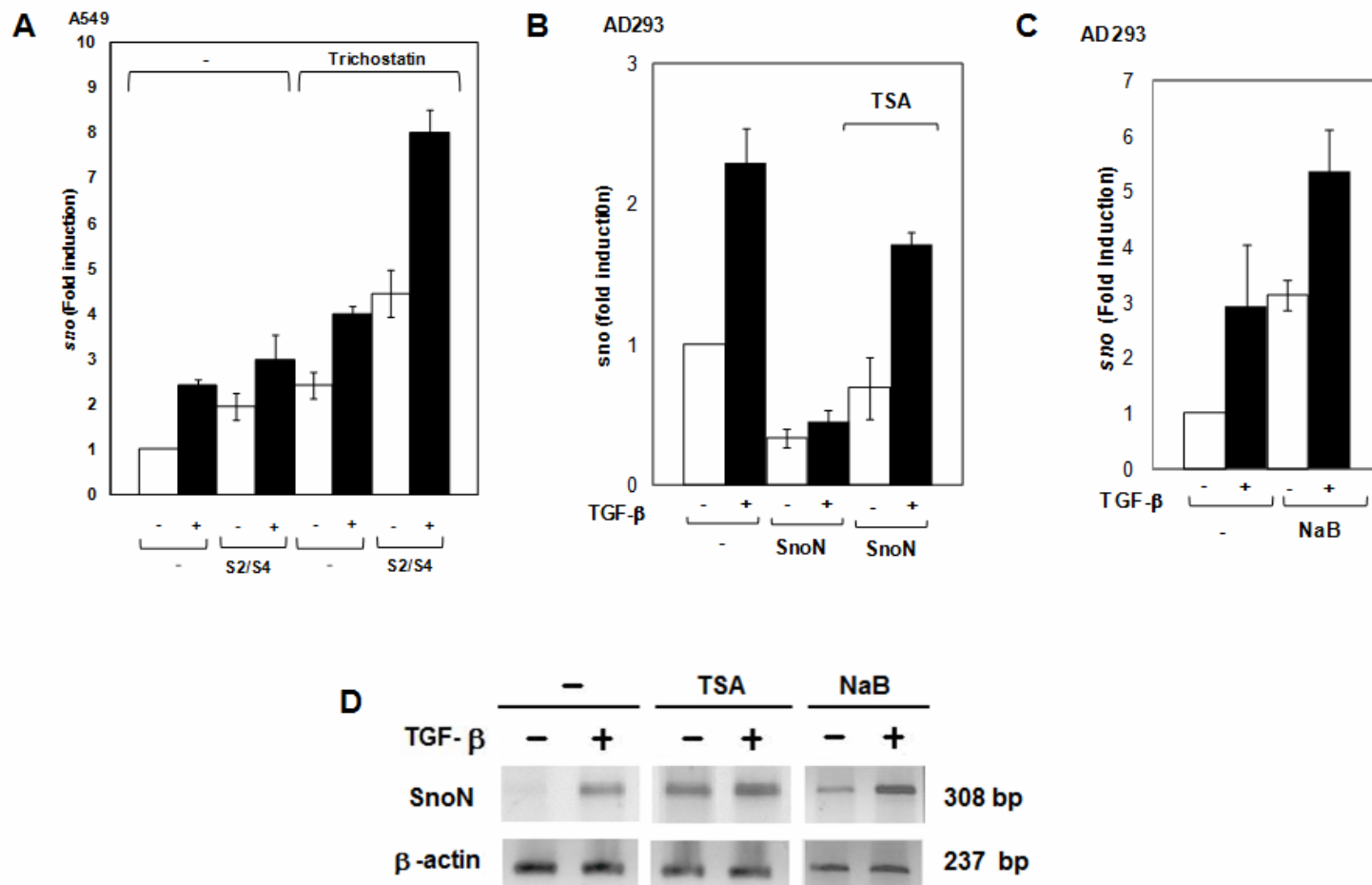
snoSBEs-Luc



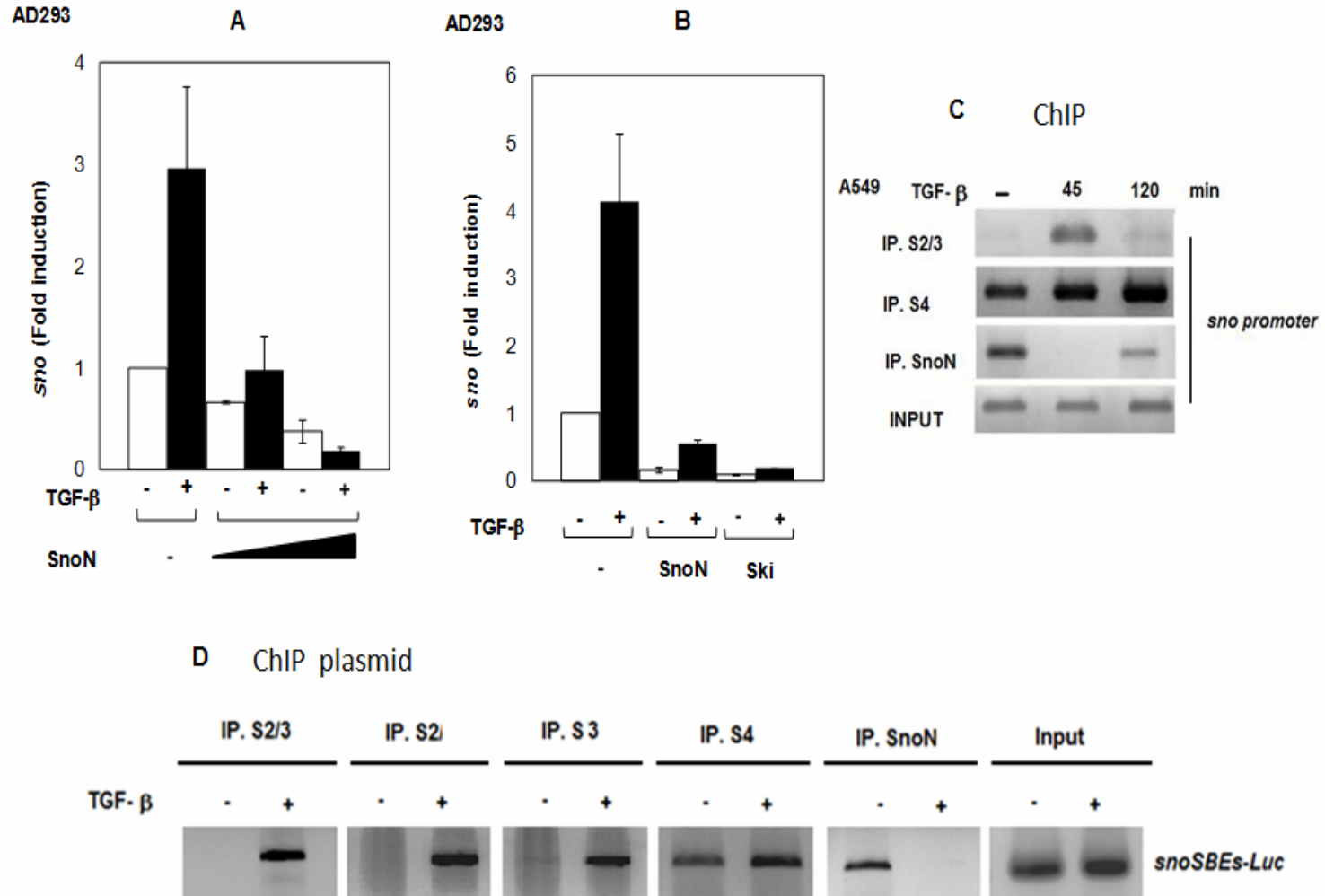
Regulación del gen *sno* por Ski y SnoN



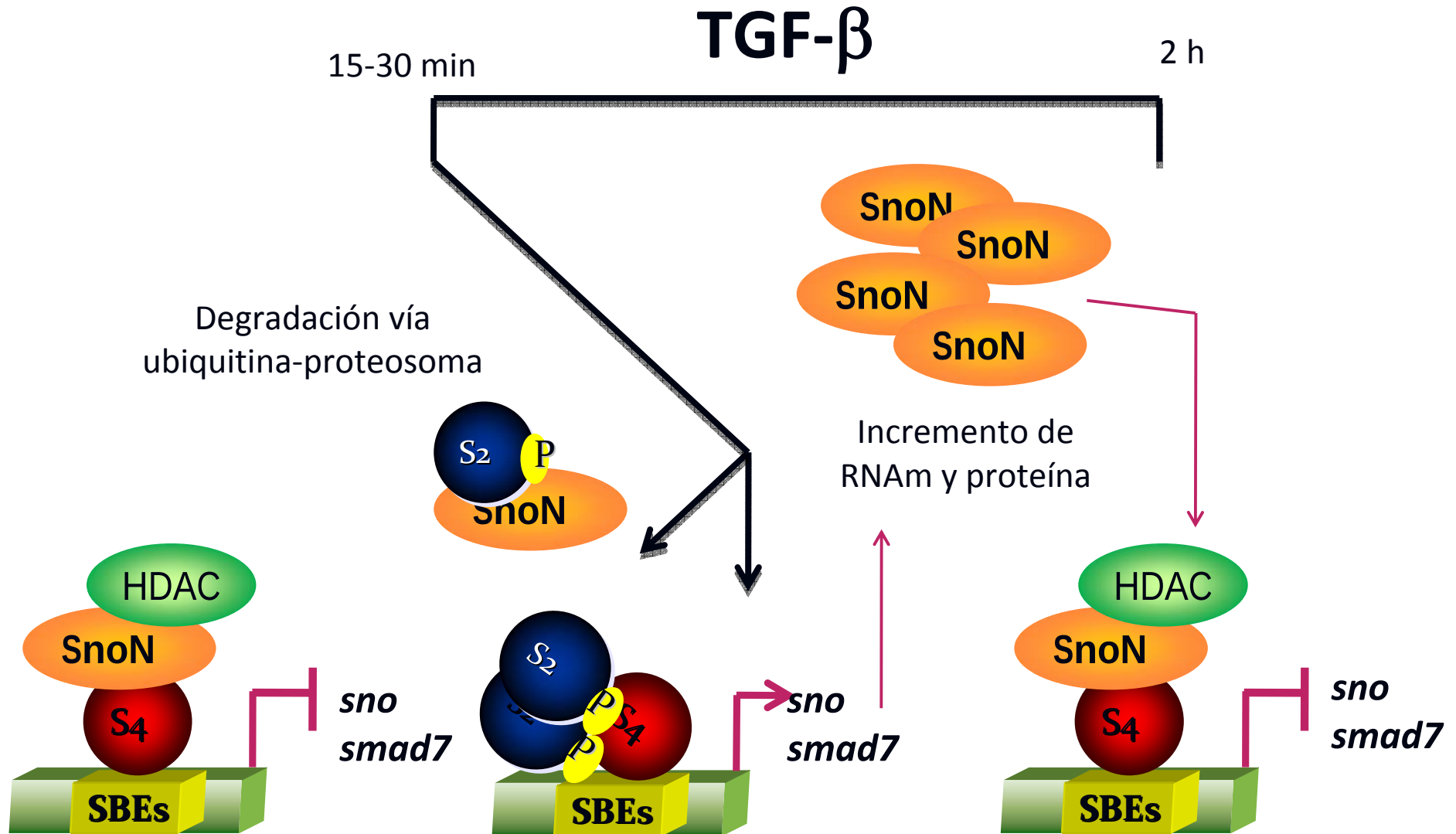
Regulación del gen *sno* por Ski y SnoN



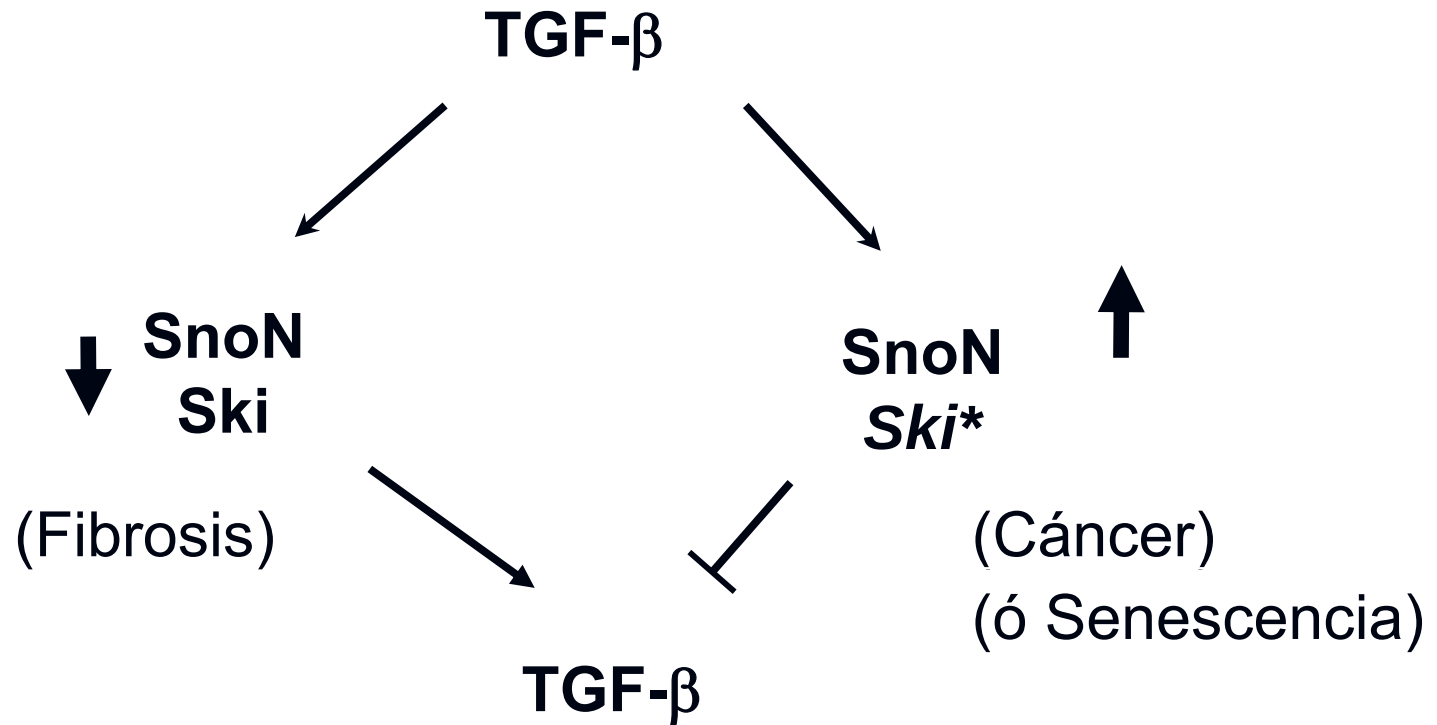
Regulación del gen *sno* por Ski y SnoN



Regulación de los genes *smad7* y *sno* por TGF- β



Regulación de los niveles de las proteínas Ski y SnoN



Relevancia del Control en los Niveles de SnoN

SNO expression	Human Diseases
high	Lymphoma
high	Malignant Melanoma
high	Breast Cancer
high	Lung Cancer
high	Esophageal Cancer
low	Renal Fibrosis

Target	Model	Effects	Source
SNON (low levels)	Heterozygous <i>Sno</i> +/- mice	Cancer	S. Ishii Lab Japan Science and Technology Corporation, Japan.
SNON (low levels)	Athymic nude mice injected with A549 or MDA-MB-231 cells previously transfected with a specific RNAi for SNON downregulation	Tumor metastasis	K. Luo Lab University of California, Berkeley, USA.
SNON (high levels)	Athymic nude mice injected with A549 or MDA-MB-231 cells overexpressing SNON.	Tumor growth	K. Luo Lab University of California, Berkeley, USA.
SNON (low levels)	T and B cells from heterozygous <i>Sno</i> +/- mice	Resistance to apoptosis and cell growth arrest	S. Pearson-White Lab Genentech, CA, USA
SNON (high levels)	SNON overexpression by transfecting <i>SNON</i> cDNA	Fibroblast transformation	K. Luo Lab University of California, Berkeley, USA.
SNON (high levels)	Transgenic mice overexpressing SNON	Muscle differentiation affected	C. Tachi Lab Azabu University, Japan

SnoN

Ratón KO *sno* (-/-)

Muere en etapas
embrionarias tempranas

Ratón *sno* (+/-)

Propenso al desarrollo
de tumores inducidos
por carcinógenos

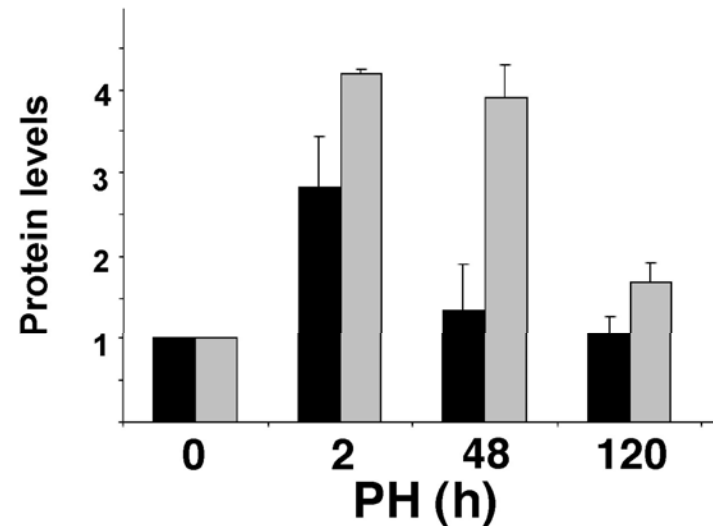
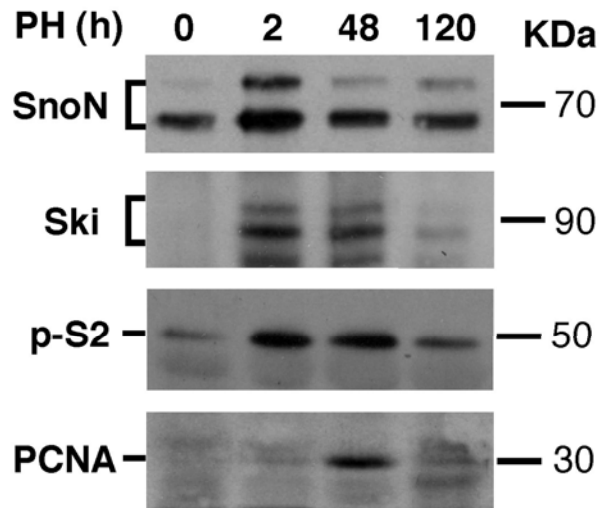
Células A549:
SnoN

SnoN favorece
la formación
de tumores

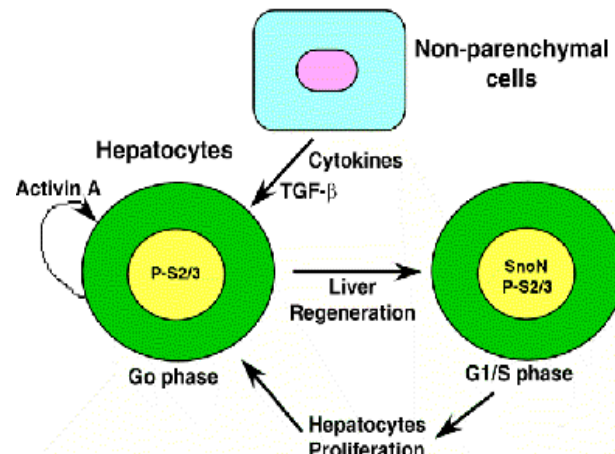
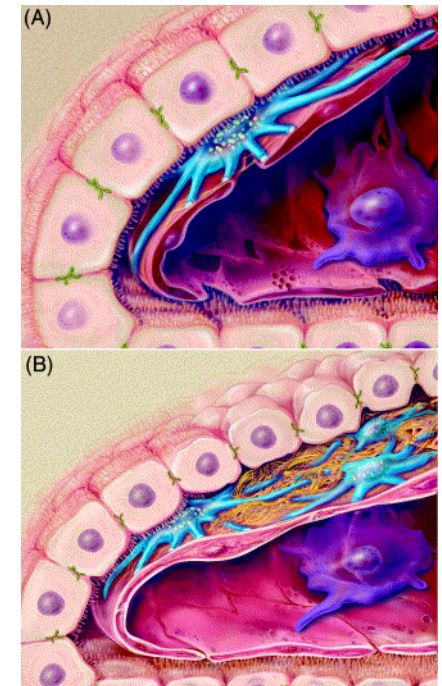


La falta de
SnoN favorece
la metastasis
de tumores

Regulación de los niveles de Ski y SnoN por el TGF- β durante la regeneración hepática



Regeneración hepática:
modelo de proliferación
celular distinto del cáncer



Instituto de Fisiología Celular, UNAM

Agradecimientos

- Angeles Tecalco
- Cassandre Caligaris
- Genaro Vázquez
- Jacqueline Hernández
- Marcela Sosa
- Paola Moreno

- Marco A. Briones
- Elisa Domínguez
- Layla Ortiz

