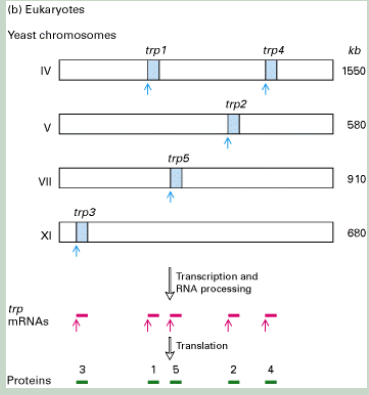
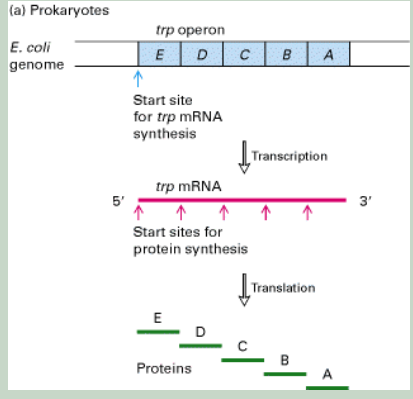
Introducción a la Biología Molecular y Celular

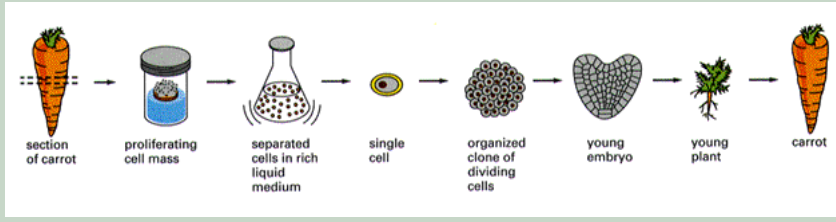
- Regulación de la Actividad Génica -

Organización genética

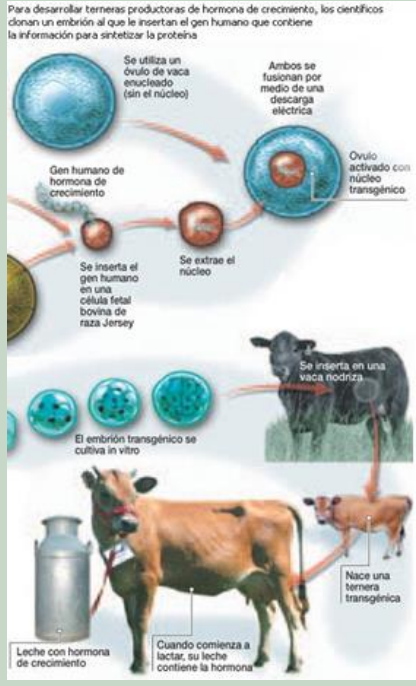




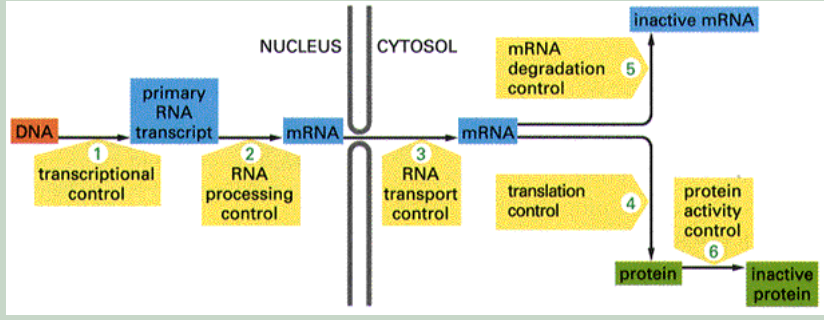
Diferenciación celular y totipotencialidad



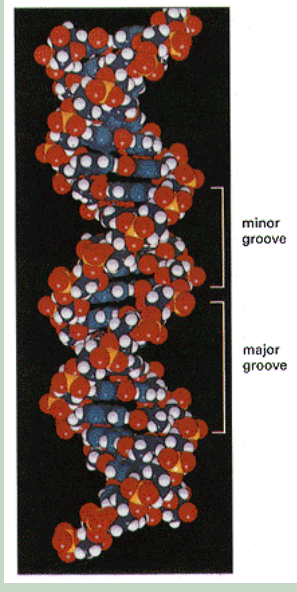
Pampita

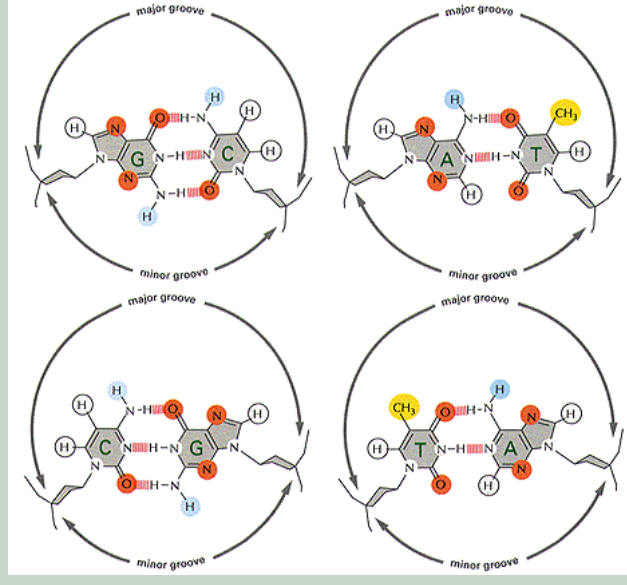


Niveles de control de la expresión génica

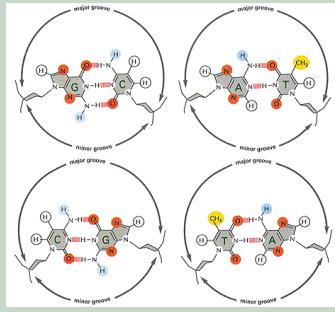


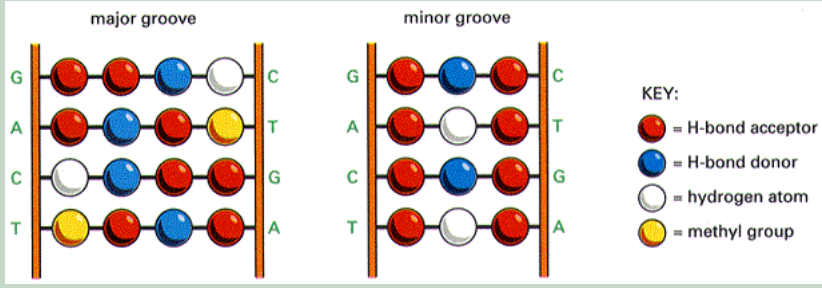
Estructura de la hélice de DNA



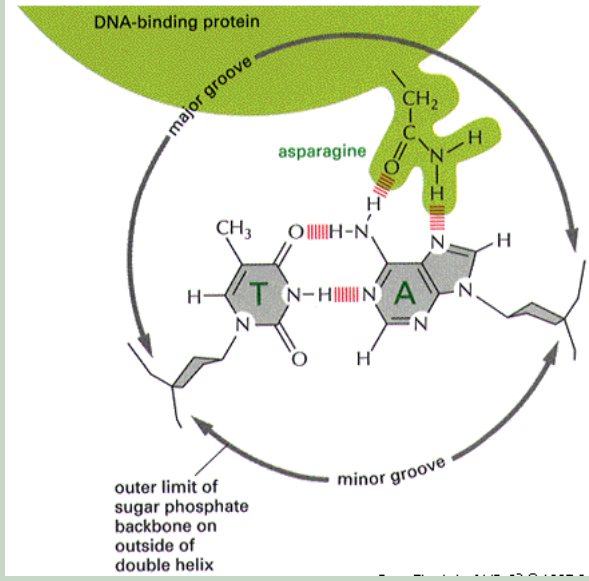


Código “conformacional”





Interacción DNA - proteína

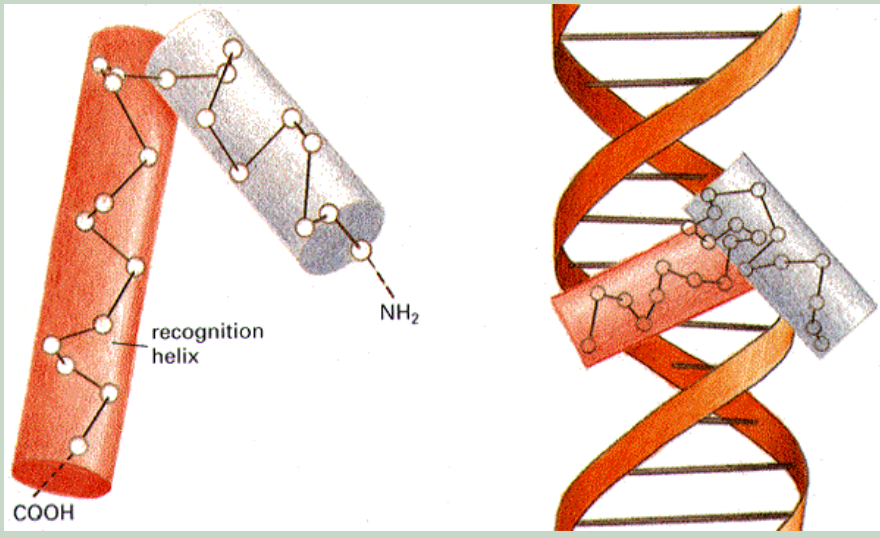


Diferentes motivos preteicos de interacción con DNA

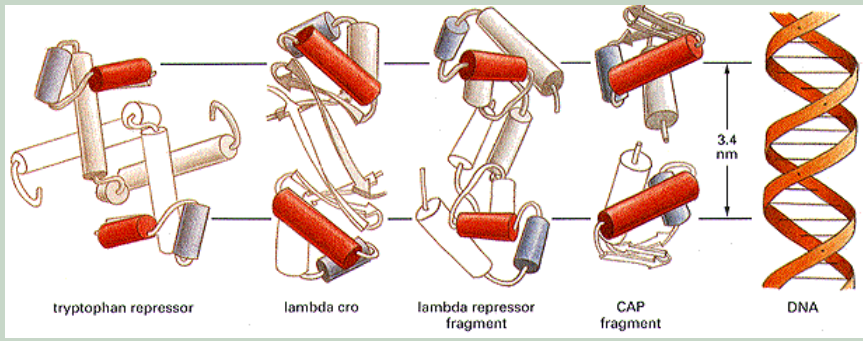
	Nombre	Secuencia de DNA reconocida*
Bacterias	represor lac	AATTGTGAGCGGATAACAATT TTAACACTCGCCTATTGTTAA
	CAP	TGTGAGTTAGCTCACT ACACTCAATCGAGTGA
	represor lambda	TATCACCGCCAGAGGTA ATAGTGGCGGTCTCCAT
Levaduras	GAL4	CGGAGGACTGTCCTCCG GCCTCCTGACAGGAGGC
	MAT α2	CATGTAATT GTACATTAA
	GCN4	ATGACTCAT TACTGAGTA
Drosophila	Krüppel	AACGGGTTAA TTGCCCAATT
	Bicoid	GGGATTAGA CCCTAATCT
Mamíferos	Sp1	GGGCGG CCCGCC
	Oct-1	ATGCAAAT TACGTTTA
	GATA-1	TGATAG ACTATC

- Hélice-Giro-Hélice
- Homeodominios
- Dedos de ZINC
- Láminas Beta
- Cremallera de Leucina
- Hélice-Bucle-Hélice

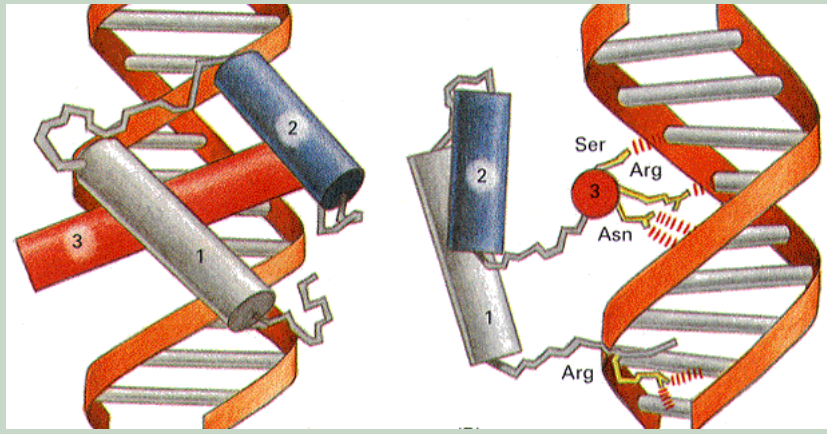
Hélice-Giro-Hélice

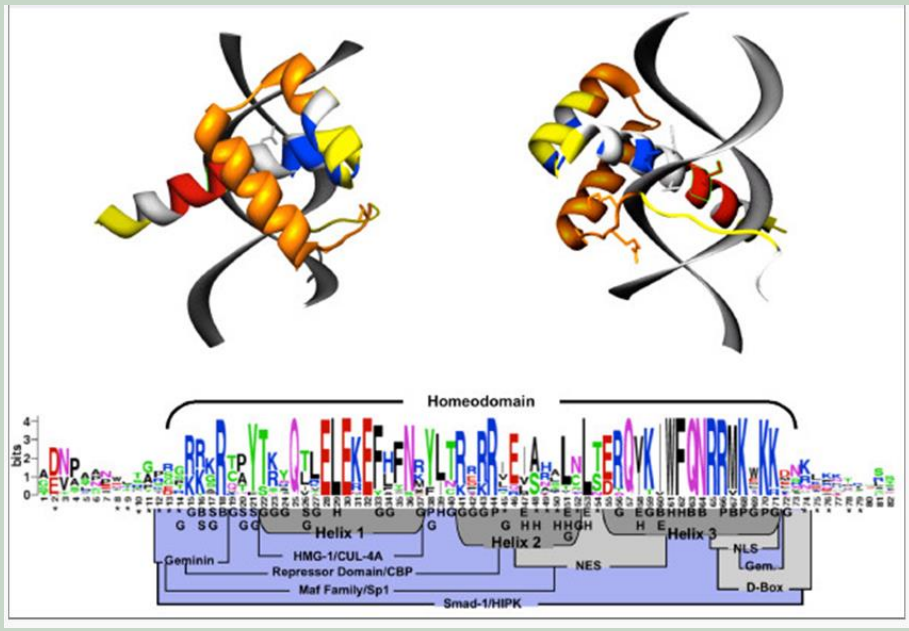


Algunos ejemplos

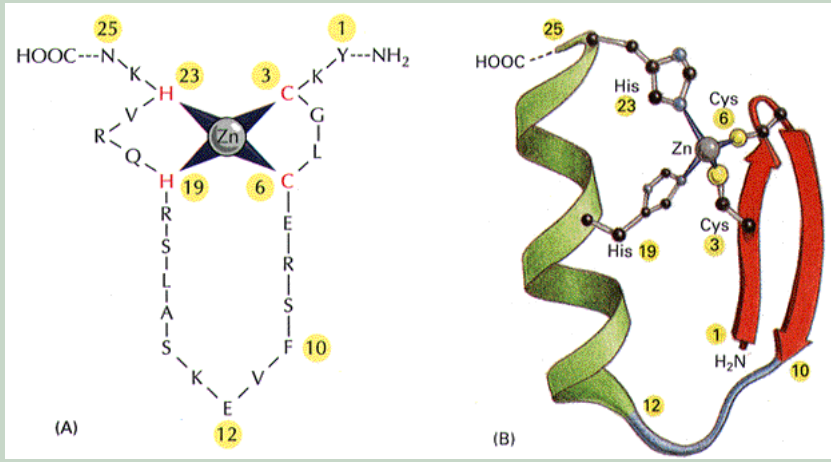


Homeodominios (euca)

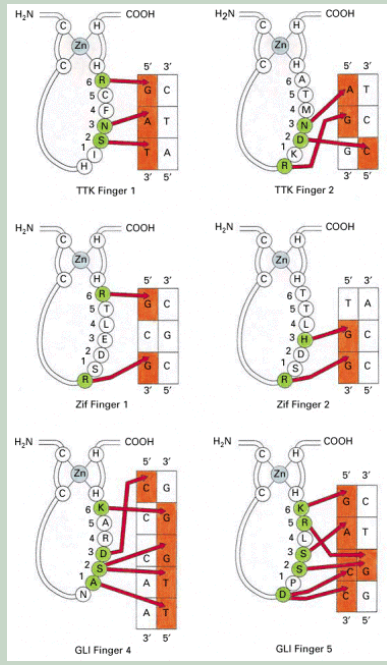




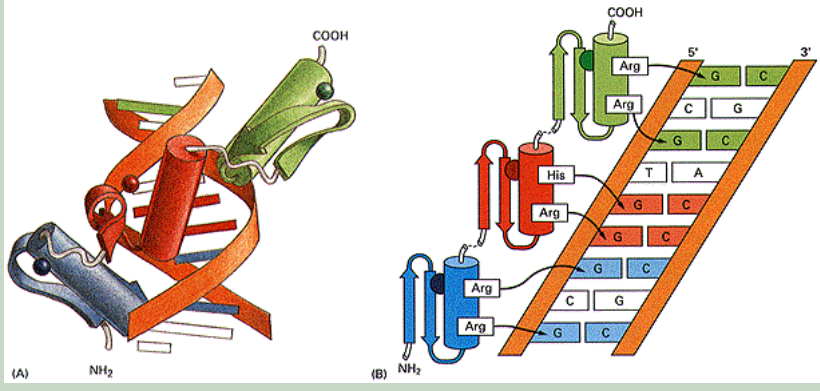
Dedos de ZINC "ZINC FINGERS"



Reconocimiento de dedos de Zink

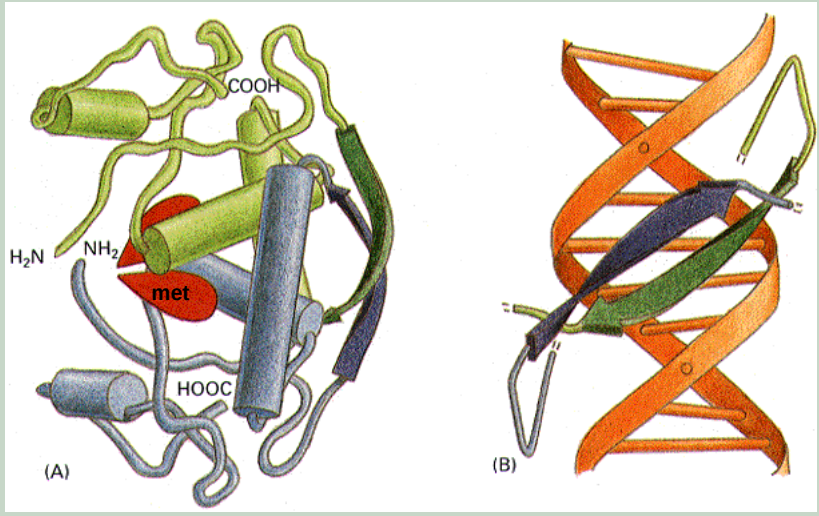


Interacción DNA – Dedos de Zinc

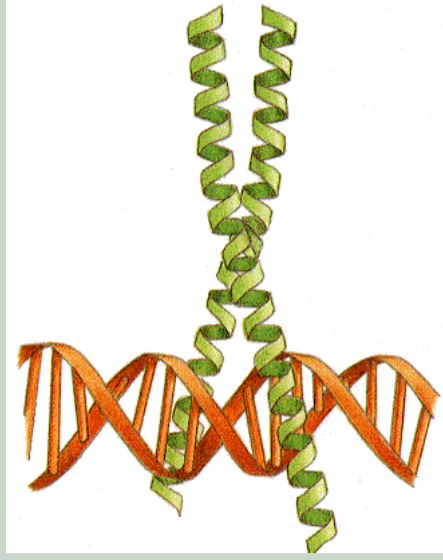


Dedos de Zinc tipo Cys-Cys-His-His

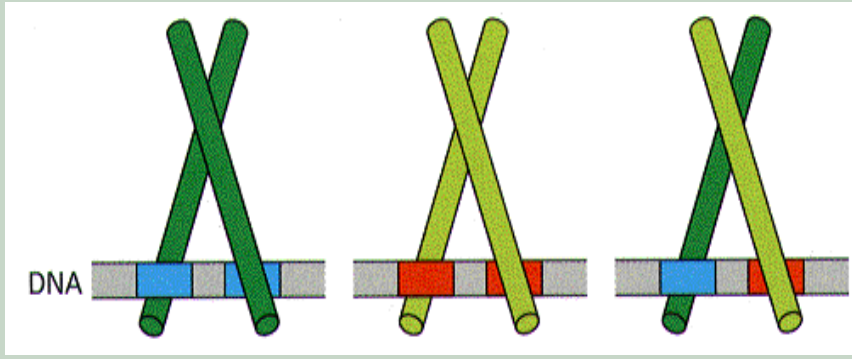
Láminas Beta



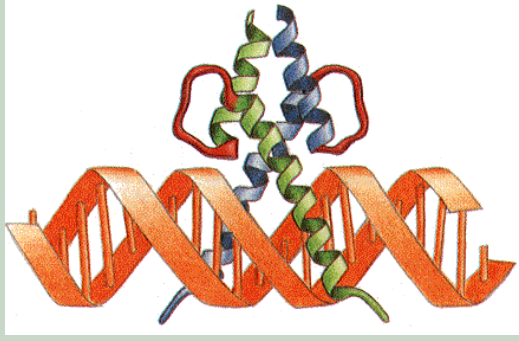
Cremallera de Leucina “LEUCINE ZIPPER”



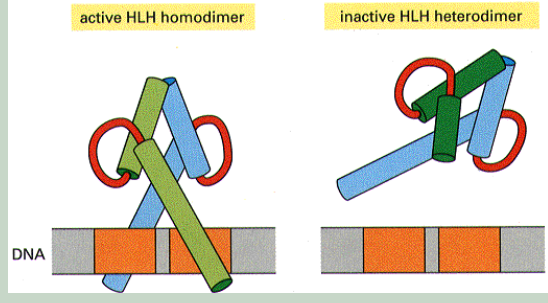
homodímeros y heterodímeros



Hélice – Bucle – Hélice. HLH: helix-loop-helix



homodímeros activos y heterodímeros inactivos

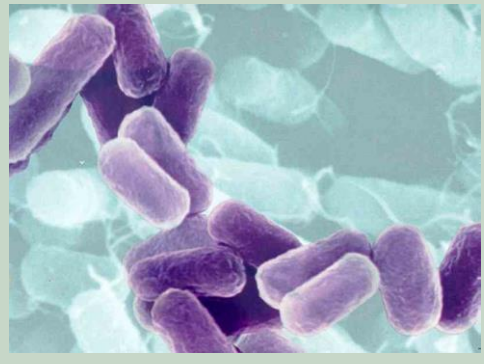


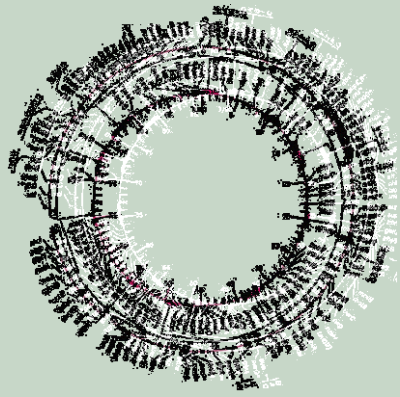
-REGULACIÓN DE LA TRANSCRIPCION EN PROCARIOTAS –

Regulación de la transcripción en procariontes

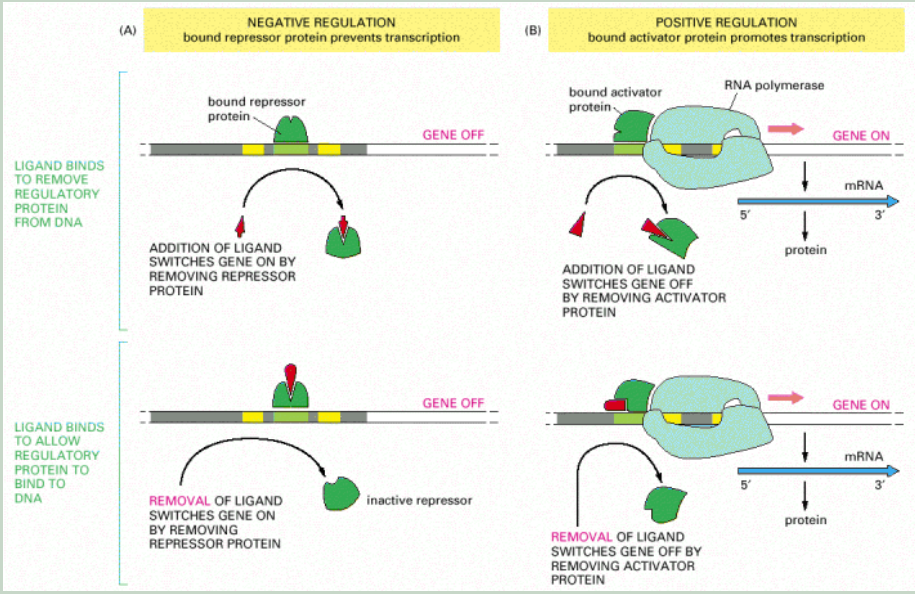
Escherichia Coli

- ADN circular de $4{,}6 \times 10^6$ pb
- 4300 proteínas

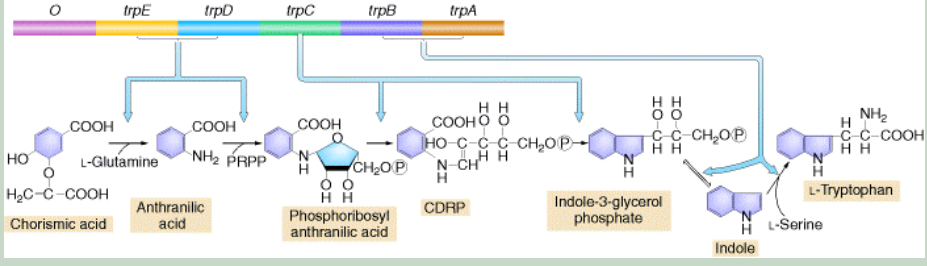




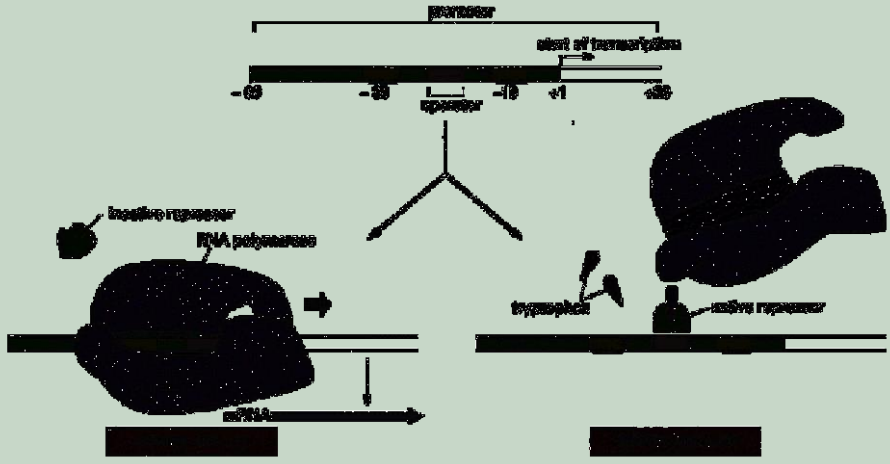
Regulación por ligando



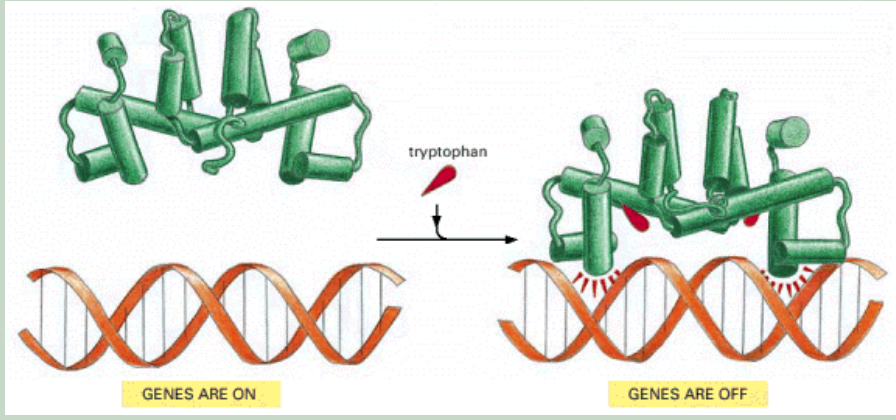
Operón triptofano



Operón triptofano



Operón triptofano



Operón lactosa

Este trabajo es considerado uno de los pioneros en el estudio del control de la expresión génica desde el enfoque de la Biología Molecular.

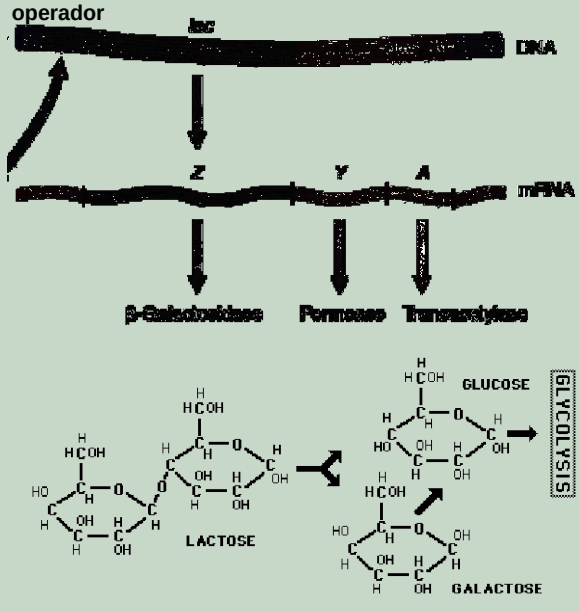
Fue considerado por las revistas cientìficas del momento como un trabajo que no cumplía los requisitos de publicación, por lo que los autores fundaron su propia reviste (the Journal of Molecular Biology) y el artìculo del Operòn Lactosa ocupaba 80 paginas del primer número.

jacob

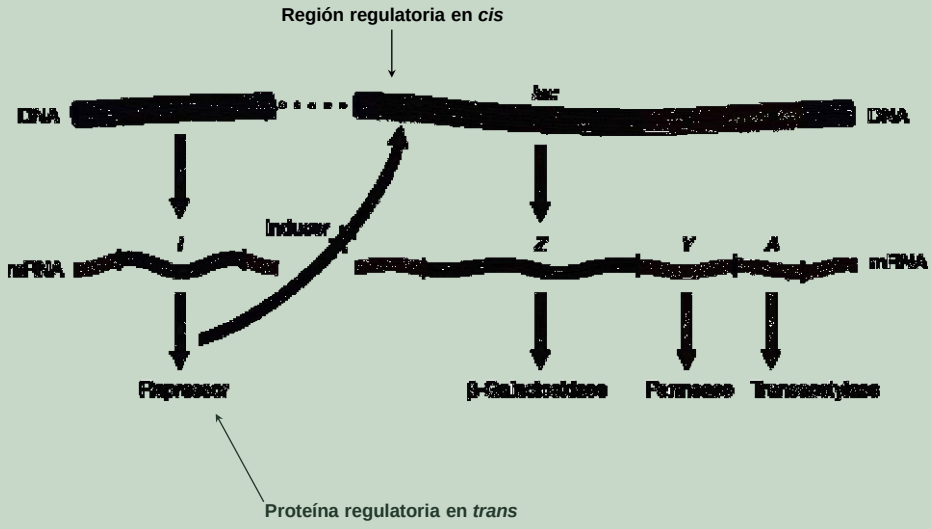
Monod

Premio Nobel de Química 1965

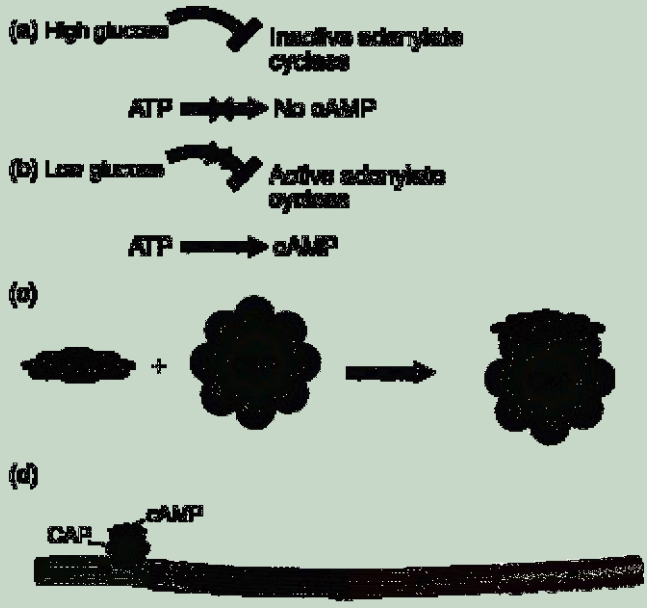
Operón lactosa



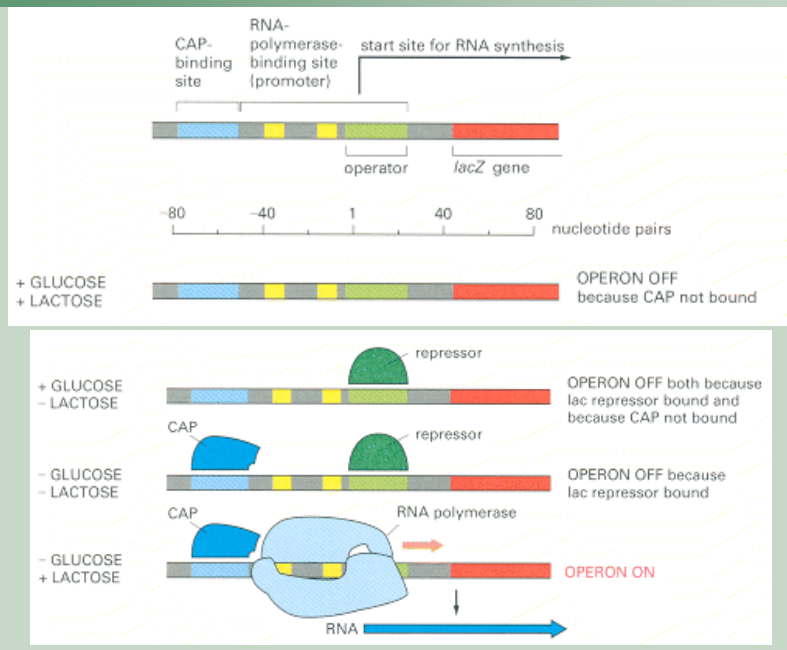
Operón lactosa



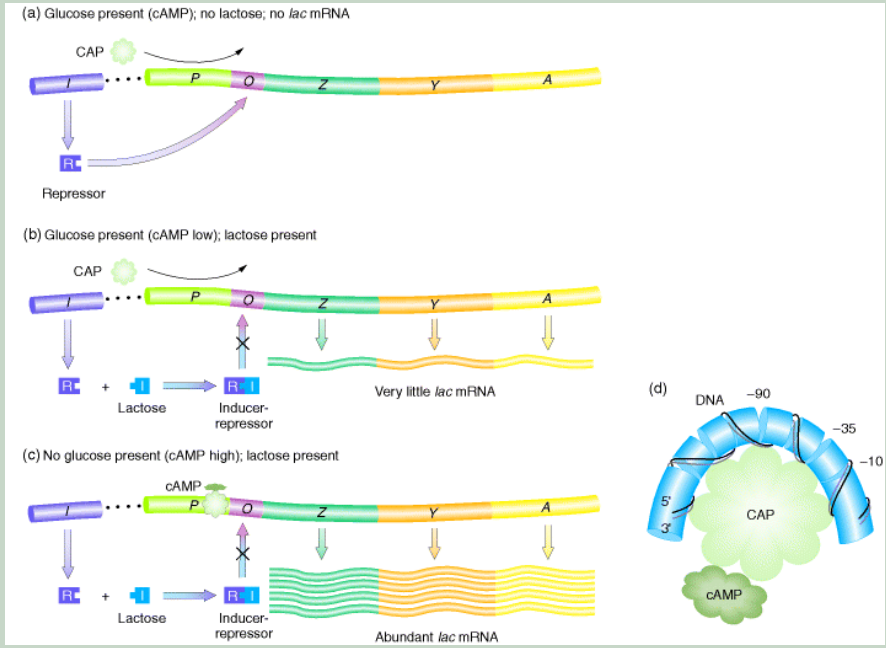
Operón lactosa



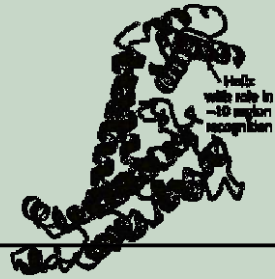
Operón lactosa



Operón lactosa



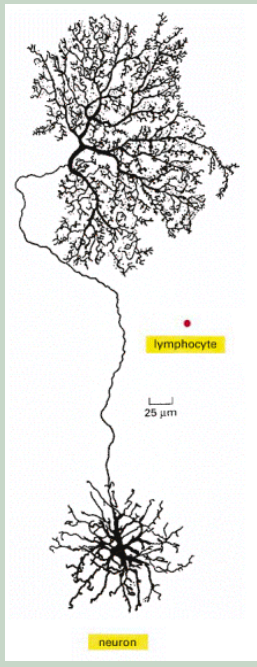
Factores sigma

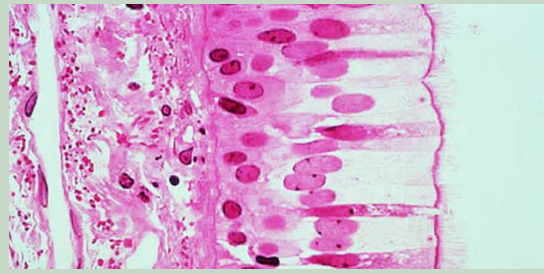


Sigma Factor	Promoters Recognized	Promoter Consensus	
		–35 Region	–10 Region
σ^{70}	Most genes	TTGACAT	TATAAT
σ^{32}	Genes induced by heat shock	TCTCNCCCTTGAA	CCCCATNTA
σ^{28}	Genes for motility and chemotaxis	CTAAA	CCGATAT
σ^{38}	Genes for stationary phase and stress response	?	?
		–24 Region	–12 Region
σ^{54}	Genes for nitrogen metabolism and other functions	CTGGNA	TTGCA

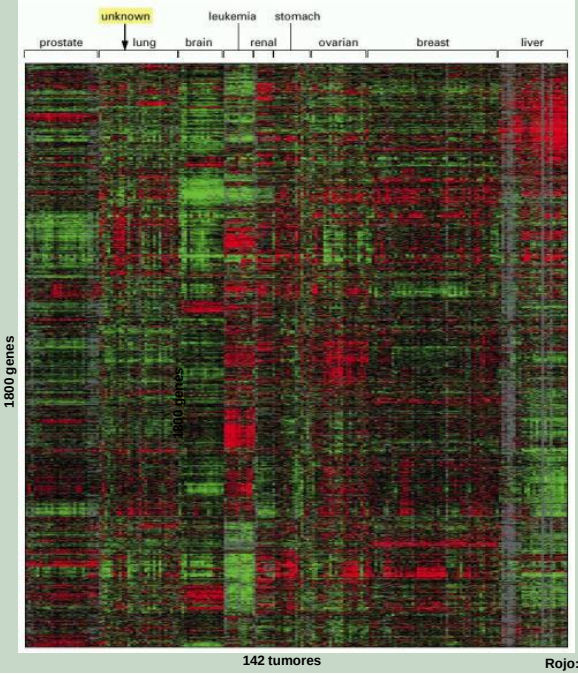
-REGULACIÓN DE LA TRANSCRIPCION EN EUCARIOTAS –

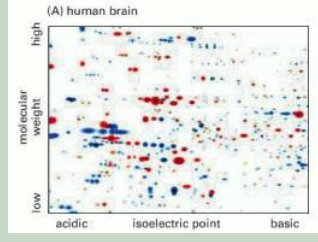
Expresión diferencial entre células

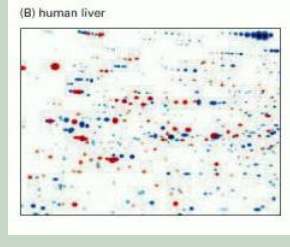




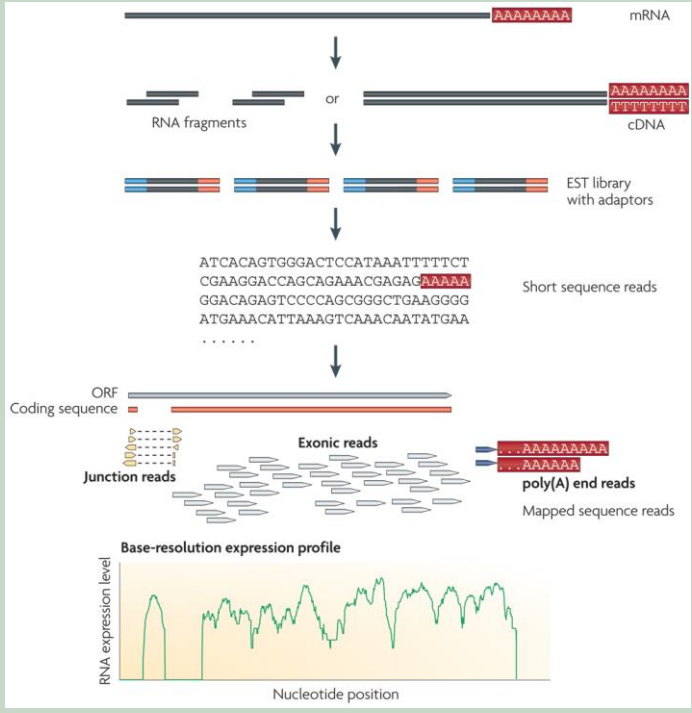
Expresión diferencial entre células



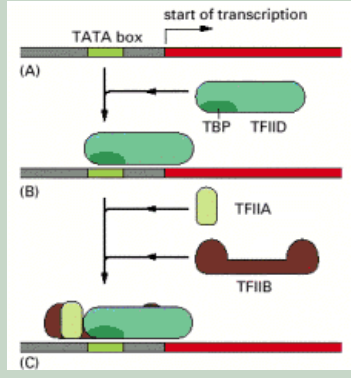


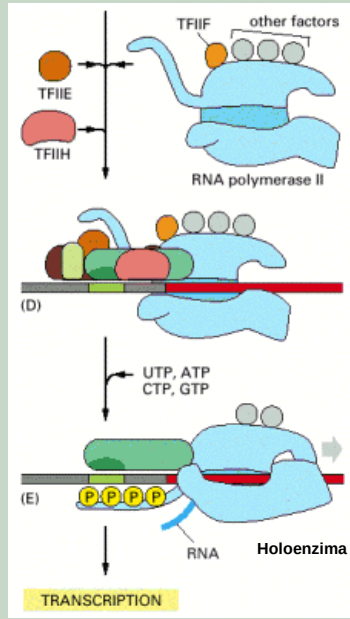


Rojo: Sobreexpresión



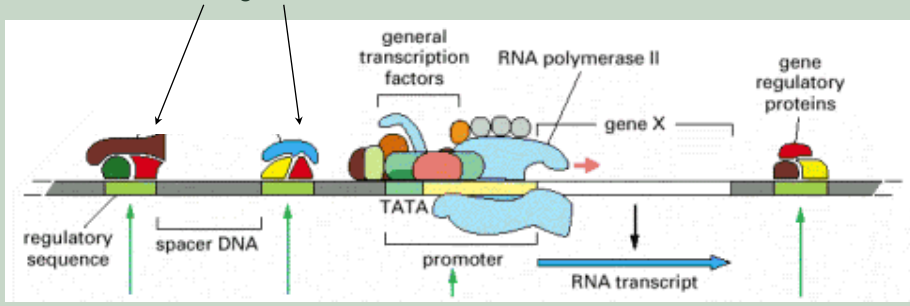
Transcripción Eucariota





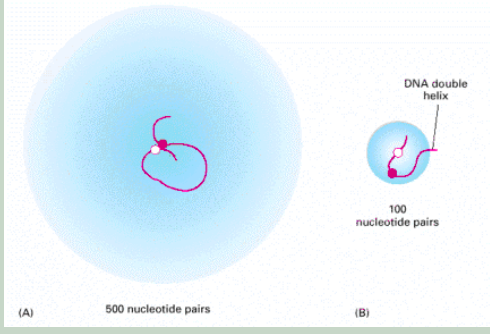
Regulación eucariota

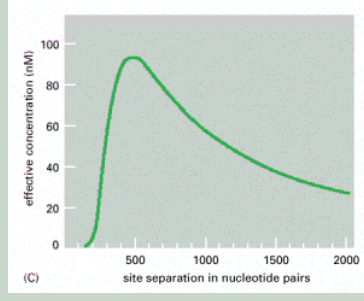
Proteínas regulatorias en *trans*

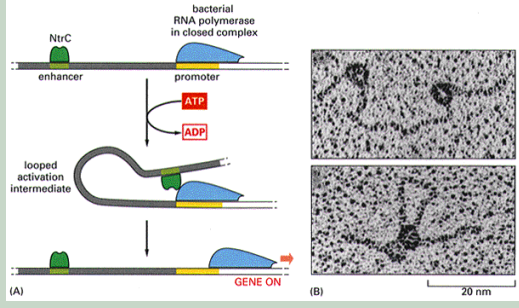


Regiones regulatorias en *cis*

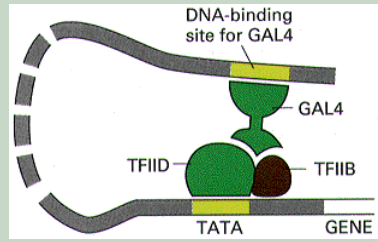
Regulación eucariota

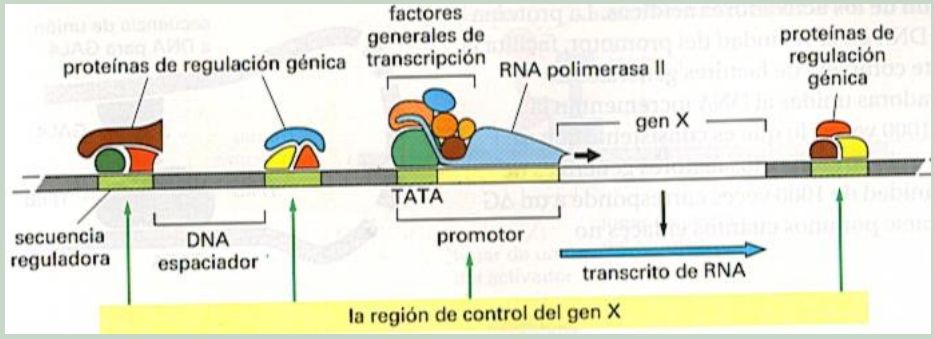




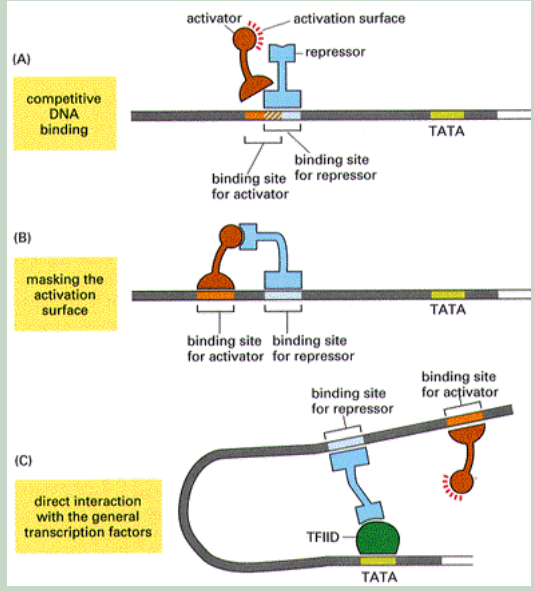


Región de control génico eucariota

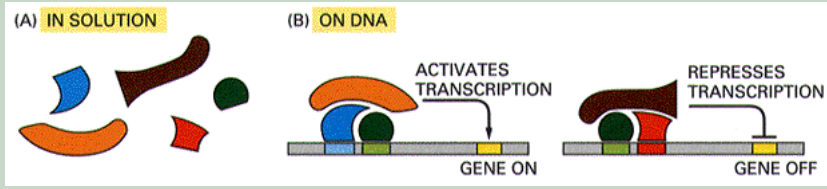




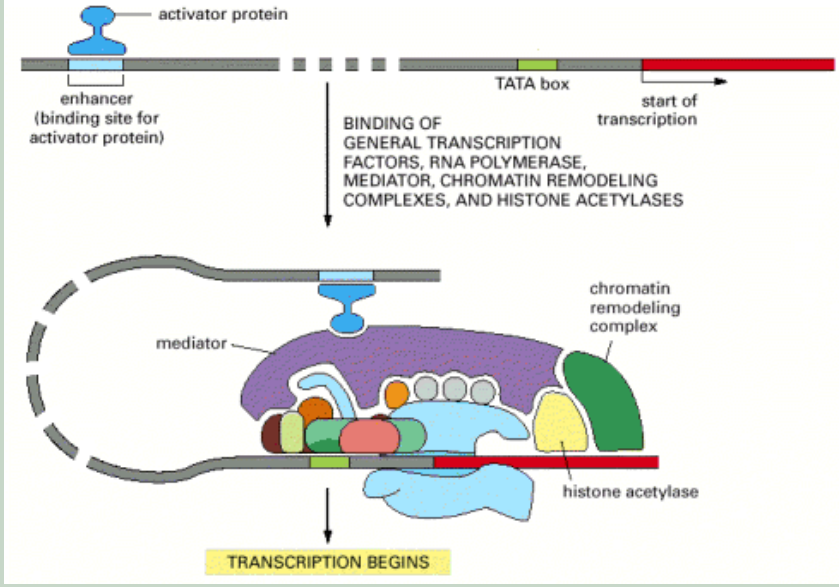
Sistemas de represión



Complejos proteicos



Regulación eucariota



Regulación eucariota

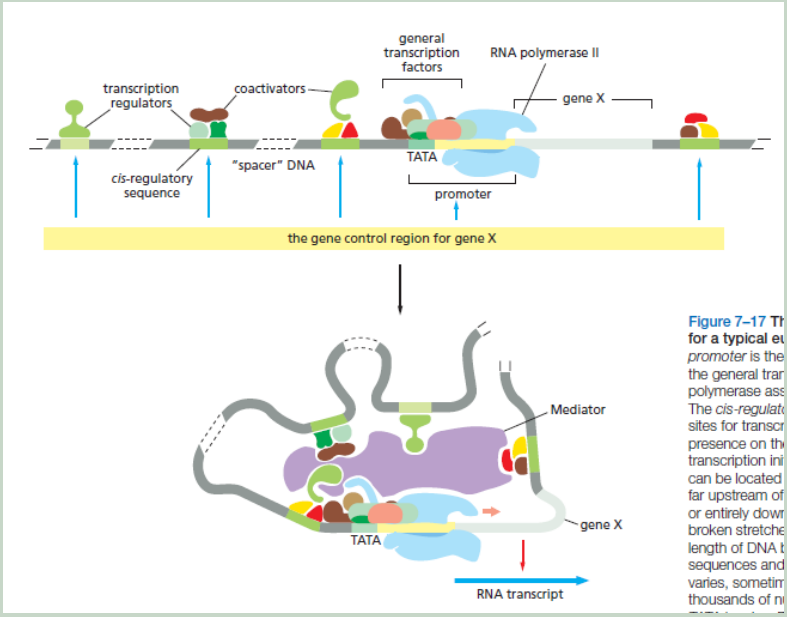
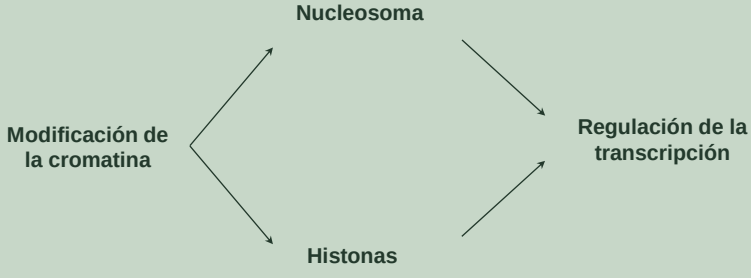
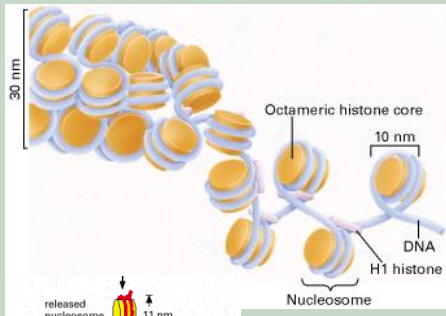


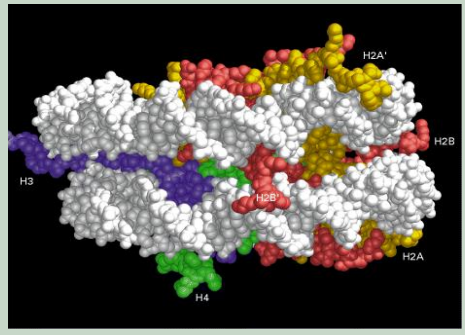
Figure 7–17 Th
for a typical eu
promoter is the
the general trar
polymerase ass
The *cis-regulat*
sites for transcr
presence on th
transcription ini
can be located
far upstream of
or entirely down
broken stretche
length of DNA t
sequences and
varies, sometim
thousands of n

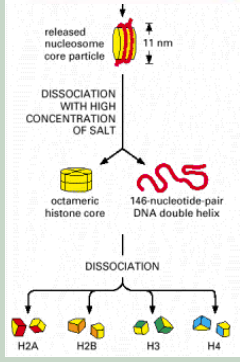
Modificacion de la cromatina

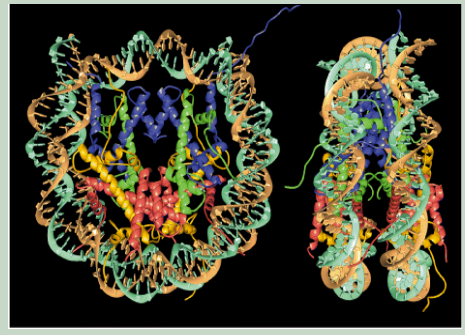


Alteraciones en el nucleosoma

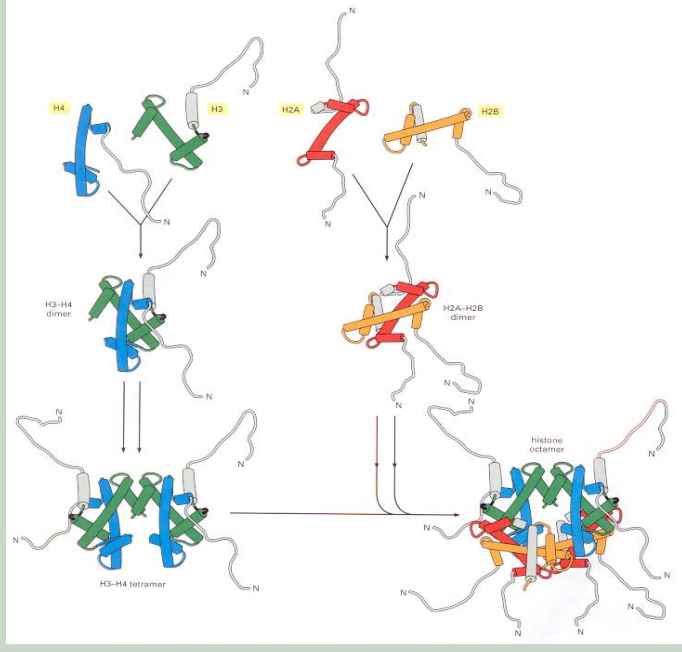




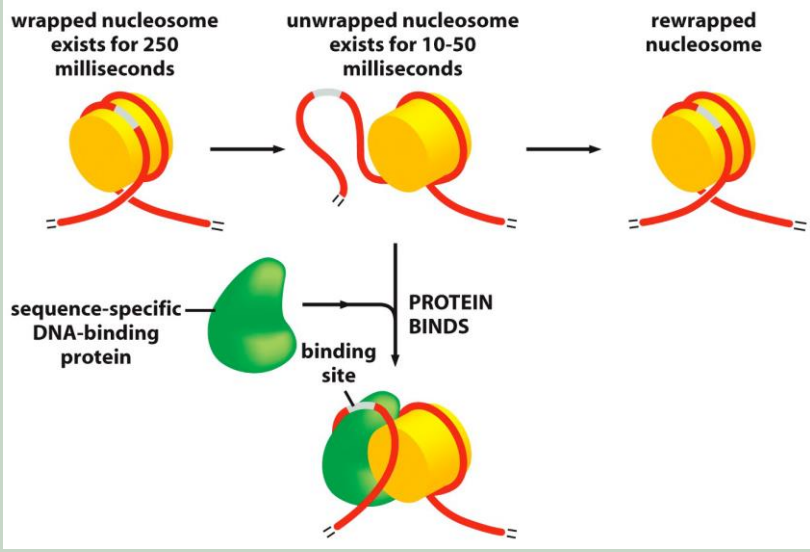


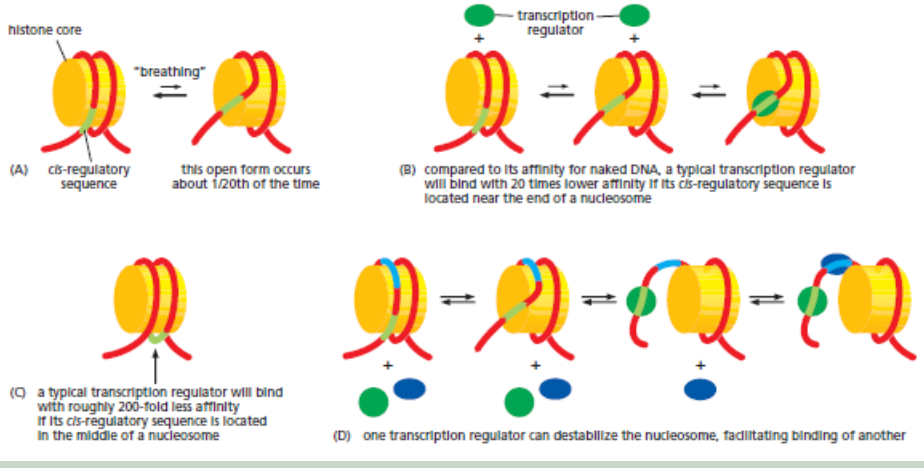


Conformación del nucleosoma

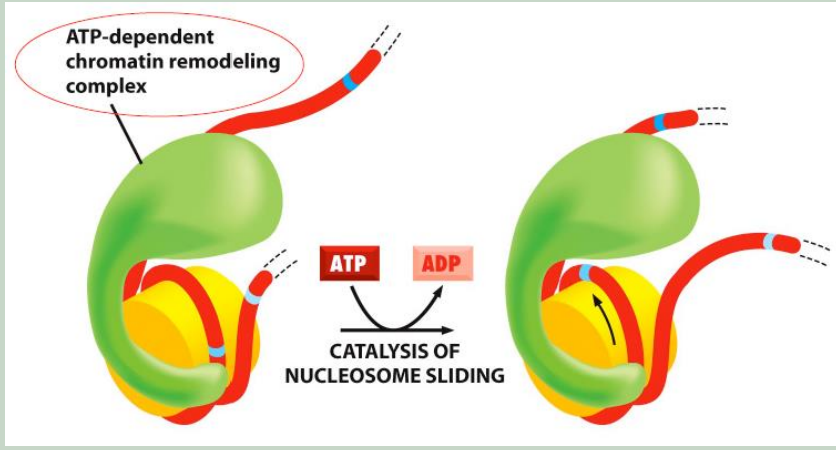


El nucleosoma es una estructura dinámica

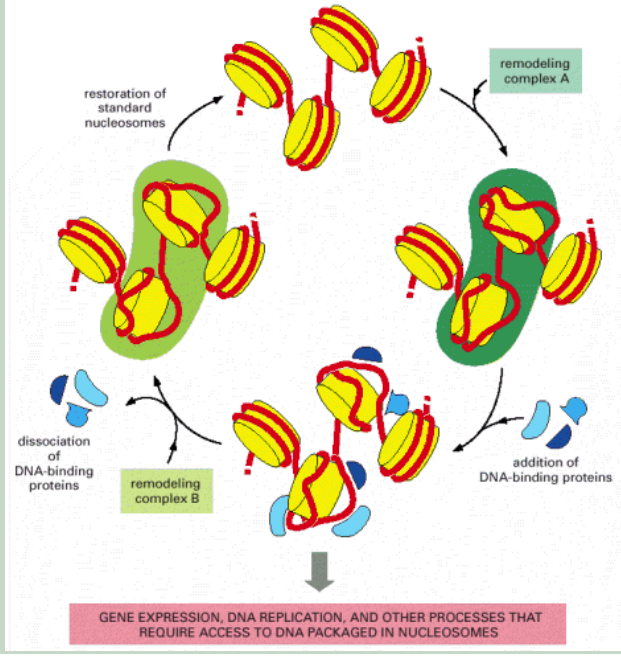




Complejo modelador de la cromatina



Modificación del nucleosoma



Variantes de histonas

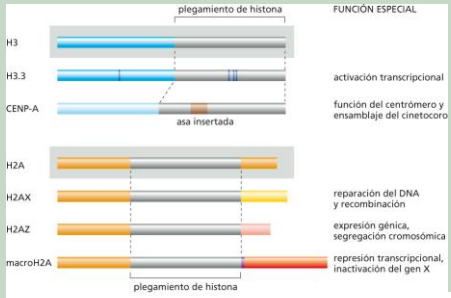


Figura 4-41 Biología molecular de la célula, quinta edición (© Garland Science 2008 y Ediciones Omega 2010)

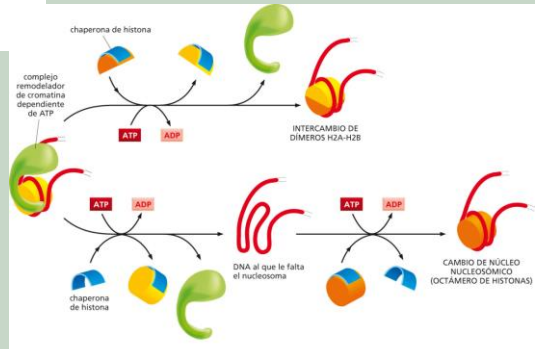
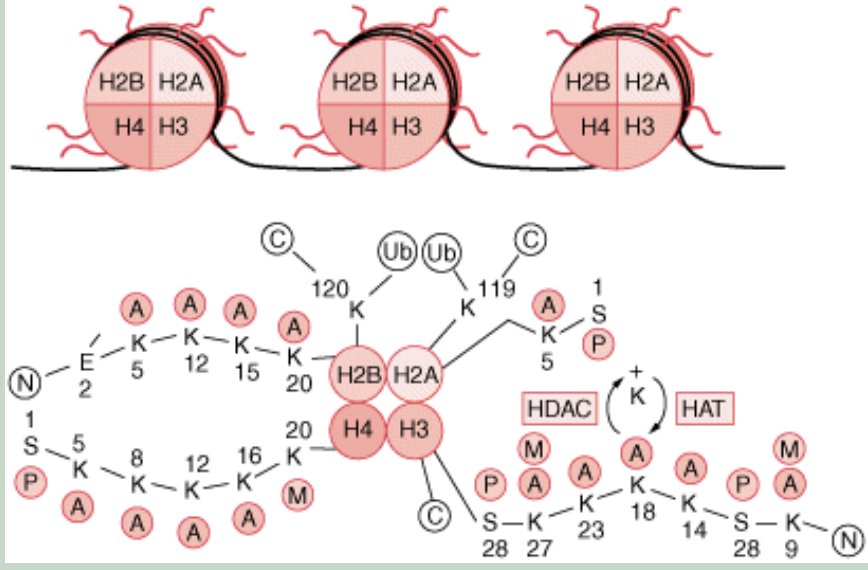
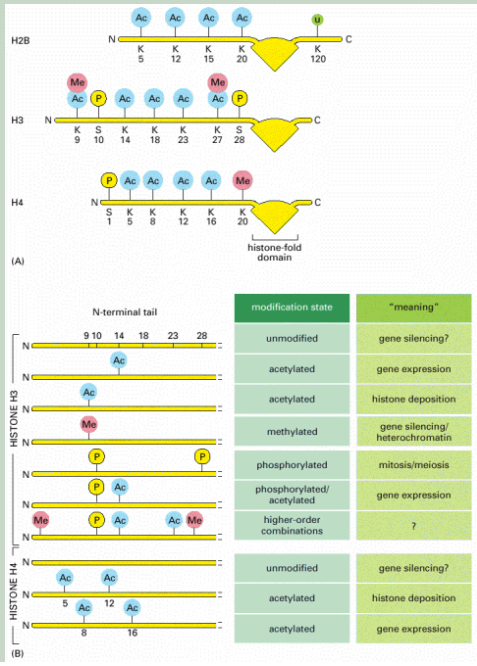


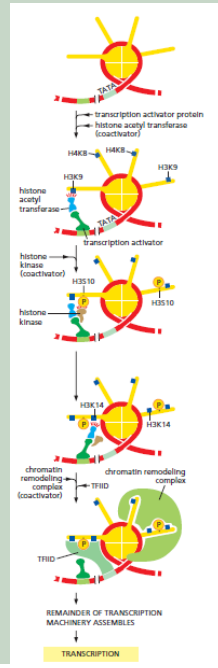
Figura 4-30 Biología molecular de la célula, quinta edición (© Garland Science 2008 y Ediciones Omega 2010)

Acetilación de Histonas



Acetilación de Histonas





Código de histonas

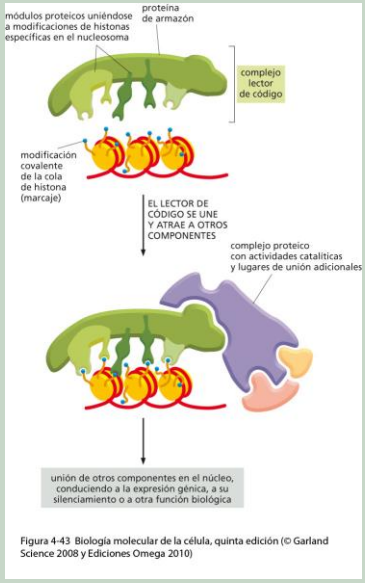


Figura 4-43 Biología molecular de la célula, quinta edición (© Garland Science 2008 y Ediciones Omega 2010)

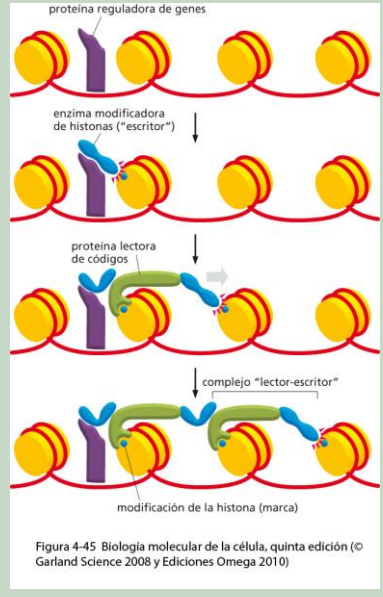
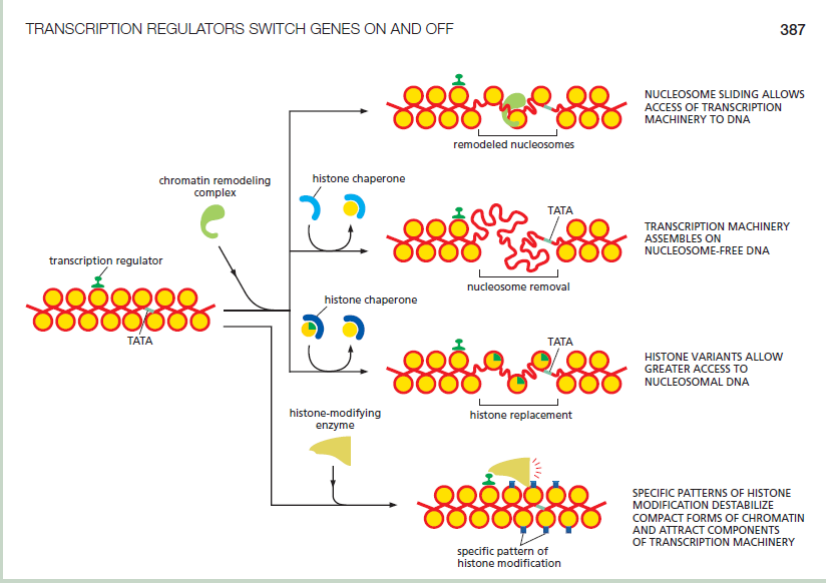
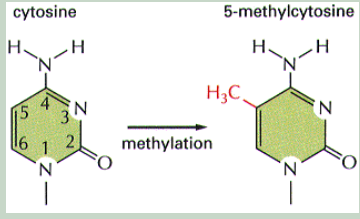
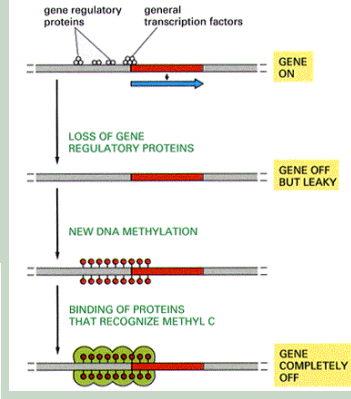


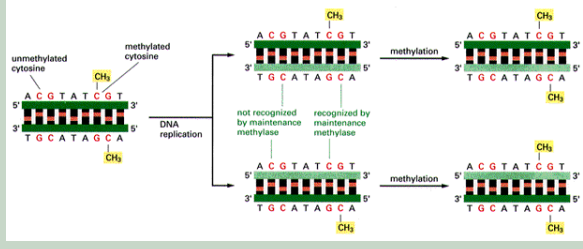
Figura 4-45 Biología molecular de la célula, quinta edición (© Garland Science 2008 y Ediciones Omega 2010)

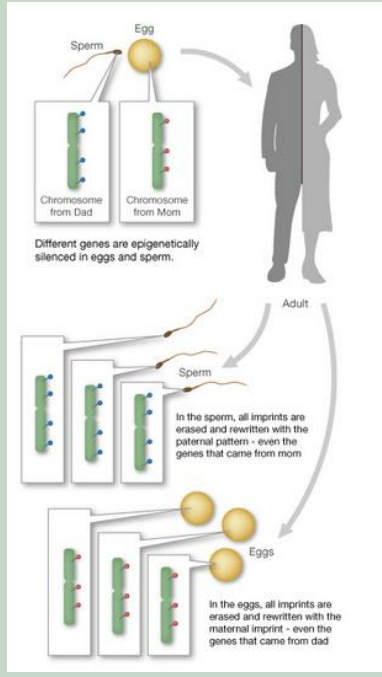


Metilación del DNA









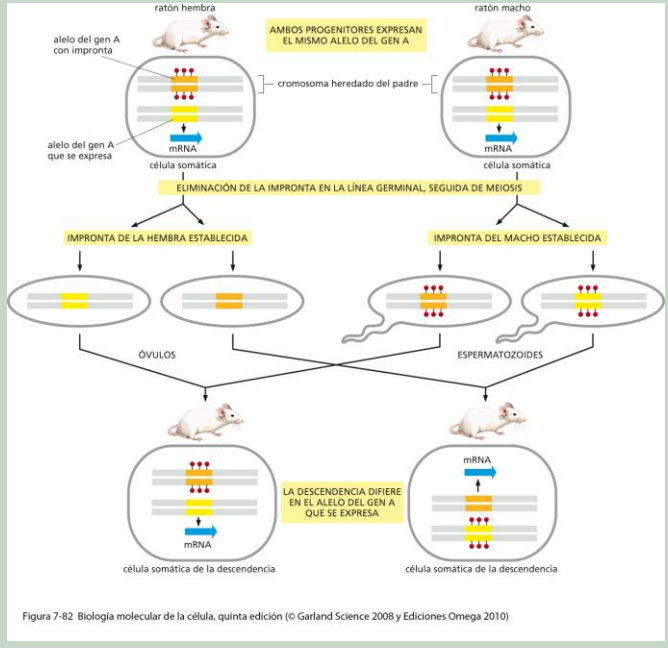
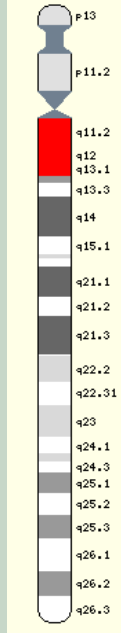


Figura 7-82 Biología molecular de la célula, quinta edición (© Garland Science 2008 y Ediciones Omega 2010)

Genomic imprinting

Prader–Willi syndrome
(androgenones)



Angelman syndrome
(gynogenones)

American Journal of Medical Genetics Part C (Seminars in Medical Genetics) 154C:365–376 (2010)

ARTICLE

Prader–Willi Syndrome and Angelman Syndrome

KARIN BUITING*

INTRODUCTION

The Prader–Willi syndrome (PWS) and Angelman syndrome (AS) are the first known examples of human diseases involving imprinted genes. Each occurs with a frequency of ~1:15,000–1:25,000 live births. De novo interstitial deletions of the same chromosome region [del(15)(q11q13)] in patients with PWS and AS, were first identified by high-resolution chromosome banding and later confirmed by molecular studies [Ledbetter et al., 1981; Kaplan et al., 1987; Magenis et al., 1987; Donlon, 1988; Knoll et al., 1989; Tantravahi et al., 1989; Nicholls et al., 1989a]. At that time it was hard to explain why indistinguishable deletions of the same chromosomal region could lead to two clinically distinct disorders, each with characteristic cognitive, behavioral, and neurologic phenotypes. The first evidence for a parent-of-origin effect came from a study performed by Butler and Palmer [1983], who demonstrated, by studying the inheritance of chromosomal polymorphisms, that the deletion always occurs on the chromosome 15 inherited from the father. This finding was confirmed at the molecular level by Knoll et al. [1989], who also demonstrated that chromosome 15q11q13 deletions in AS always occur on the maternal chromosome. Based on the study of polymorphic DNA markers, Nicholls et al. [1989b] provided the first evidence that some PWS individuals inherit both chromosome 15s from the mother. The first patients with AS and a paternal uniparental disomy were identified by Malcolm et al. [1991] indicating that AS results from the absence of the maternal contribution of at least one gene in the chromosomal region 15q11q13. And indeed, further studies revealed that the chromosomal region 15q11–q13 contains a cluster of genes that are expressed from the paternal or maternal chromosome only. It is now known that AS results from the loss of function of the *UBE3A* gene, which in brain is expressed from the maternal chromosome only [Kishino et al., 1997; Matsuura et al., 1997]. In PWS, the situation is less clear, but a deficiency of the paternally expressed *SNORD116* snoRNAs can result in a PWS or PWS-like phenotype [Sahoo et al., 2008;

It is now known that AS results from the loss of function of the UBE3A gene, which in brain is expressed from the maternal chromosome only. In PWS, the situation is less clear, but a deficiency of the paternally expressed SNORD116 snoRNAs can result in a PWS or PWS-like phenotype.

Represión de la transcripción en eucariontes

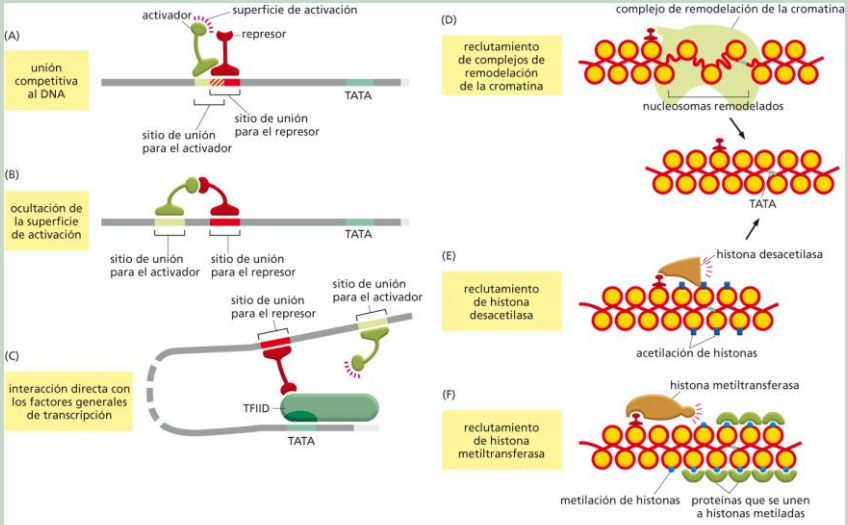
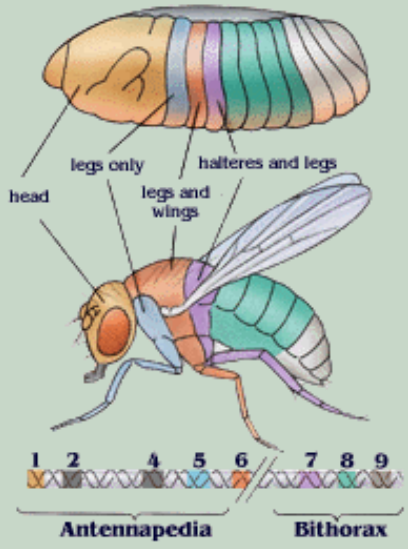
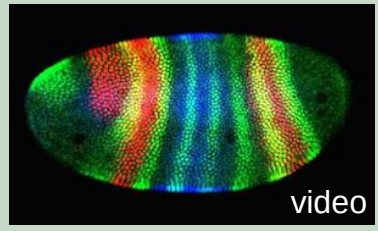


Figura 7-50a Biología molecular de la célula, quinta edición (© Garland Science 2008 y Ediciones Omega 2010)

Regulación por genes homeoticos





Comparten una seq de alrededor de 60 aa (homeodominio)

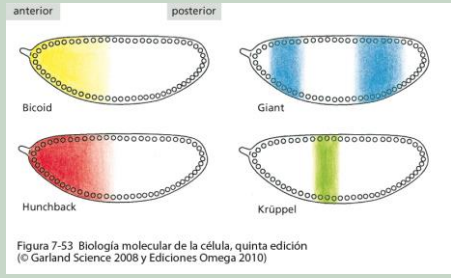
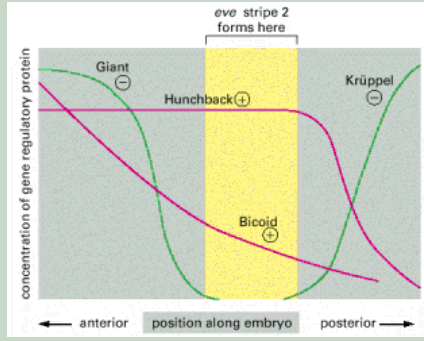


Figura 7-53 Biología molecular de la célula, quinta edición (© Garland Science 2008 y Ediciones Omega 2010)



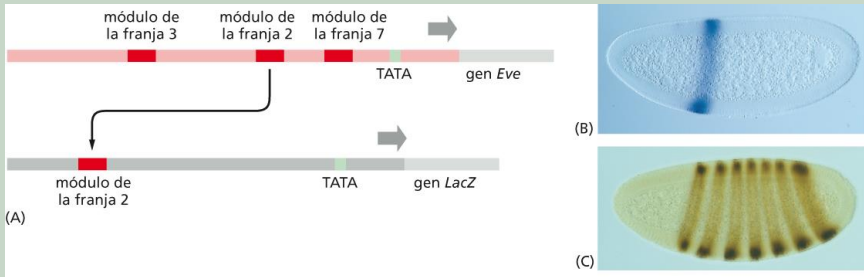
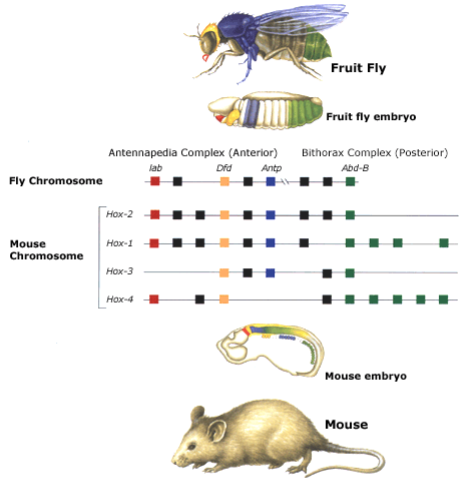


Figura 7-55a Biología molecular de la célula, quinta edición (© Garland Science 2008 y Ediciones Omega 2010)

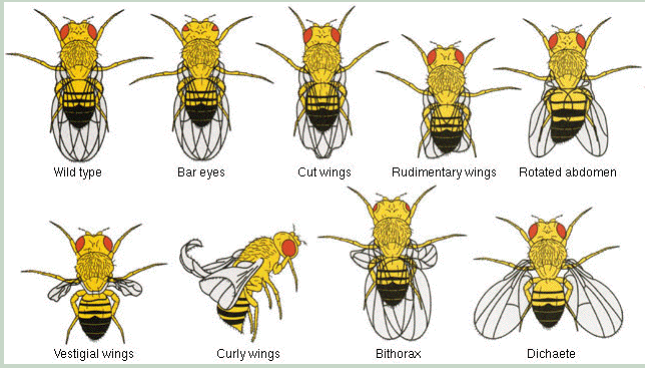
HEADS OR TAILS? FLIES AND MICE SHARE GENES THAT CONTROL BODY PATTERNS

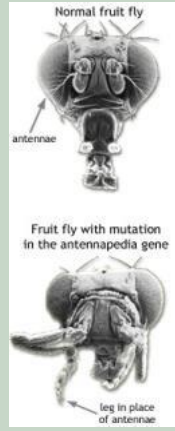


In insects and mammals, very similar genes—in the same order—control the development of front and back parts of the body.

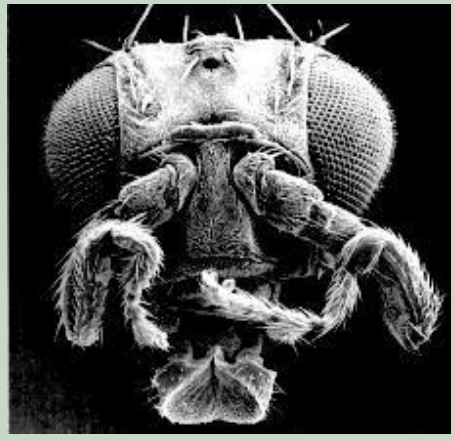
These homeobox-containing genes lie on a single chromosome in the fly (top row of colored squares). Mammals have four similar gene clusters that lie on four separate chromosomes (lower rows of squares).

The genes are color-coded to match the parts of the body in which they are expressed.


Wild type
Bar eyes
Cut wings
Rudimentary wings
Rotated abdomen
Vestigial wings
Curly wings
Bithorax
Dichaete


Normal fruit fly
antennae
Fruit fly with mutation
in the antennapedia gene
leg in place
of antennae


SPL



Introduction

Disorder of sex development (DSD) is defined as congenital condition in which the development of chromosomal, gonadal or anatomic sex is atypical (1). The incidence of DSD is 1:4500 to 1:5000 live births (2, 3). It is a social emergency as the decision-making in relation to sex assignment has been perceived as extremely disturbing and difficult to both families and health care professionals (4). Management of patients with DSD requires a co-ordinated approach by a team of an endocrinologist, a paediatrician, a surgeon, a radiologist, with good laboratory setup. Virilization of external genitalia at birth depends upon intra-uterine exposure to androgens which can be testicular, adrenal or sometimes exogenous in origin. The presence of Mullerian structures in general suggests either a female genetic sex or gonadal dysgenesis in a genetic male with inadequate production of anti-Mullerian hormone (AMH). Sex of rearing depends on the genetic sex, degree of virilization of external genitalia, prospects of restoring normal appearance of external genitalia and fertility and parent's/patient's preferences.

Table 1 Overview of various aetiologies in 194 patients of DSD.

46,XX DSD	*n* (%)	46,XY DSD	*n* (%)	Sex chromosome DSD	*n* (%)
CAH	52 (70.3)	Androgen insensitivity syndrome	32 (31.4)	Mixed gonadal dysgenesis	5 (71.4)
Ovotesticular	8 (10.8)	Androgen biosynthetic defect	26 (25.5)	Ovotesticular	1 (14.3)
MRKH	9 (12.1)	Gonadal dysgenesis	11 (10.8)	Super male	1 (14.3)
Gonadal dysgenesis	3 (4.1)	5α-reductase deficiency	9 (8.8)		
Testicular	1 (1.4)	Idiopathic Hypospadias	9 (8.8)		
Androgen exposure in utero	1 (1.4)	Vanishing testis syndrome	7 (6.8)		
		B/L cryptorchidism	2 (1.9)		
		Ovotesticular	2 (1.9)		
		Associated with other anomalies	4 (3.9)		
Undefined			11 (5.7)		

CAH: congenital Adrenal Hyperplasia

Table 3 Clinical profile of patients with 46,XY DSD with androgen insensitivity syndrome.

Type	No.	Clinical presentation	Gender assignment	Median age at presentation (years)	Positive family history
Complete androgen insensitivity syndrome	3	Primary amenorrhea	All females	18 (18–20)	1
Partial androgen insensitivity syndrome	20	Hypospadias, micropenis, bifid scrotum, clitoromegaly	17 males, 3 females	20 (16–22)	3
Minimal androgen insensitivity syndrome	9	Gynaecomastia, infertility	All males	32 (22–65)	Nil

Table 4 Clinical profile of 11 patients with ovotesticular DSD.

Age	Mode of presentation	Karyotype	Gender identity	Sex of rearing	Gonad	
					Right	Left
2/12	Ambiguity	46,XX	Female	Female	Testis	Ovary
9	Ambiguity	46,XX	Male	Male	Ovotestis	Ovary
1.5	Ambiguity	46,XX	Female	Female	Testis	Ovotestis
2/12	Ambiguity	46,XX	Male	Male	Ovotestis	Ovary
2/12	Ambiguity	46,XY	Male	Male	Ovary	Testis
41	Abdominal pain, mass	46,XX	Male	Male	Ovotestis	Ovary
1.5	Right inguinal hernia	46,XX	Female	Female	Ovotestis	Ovary
17	Ambiguity	46,XY/47,XXY	Male	Male	Ovary	Ovotestis
23	Ambiguity	46,XX	Male	Male	Testis	Ovotestis
14	Ambiguity	46,XY	Male	Female	Ovotestis	Ovary
25	Ambiguity	46,XX	Male	Male	Testis	Ovotestis