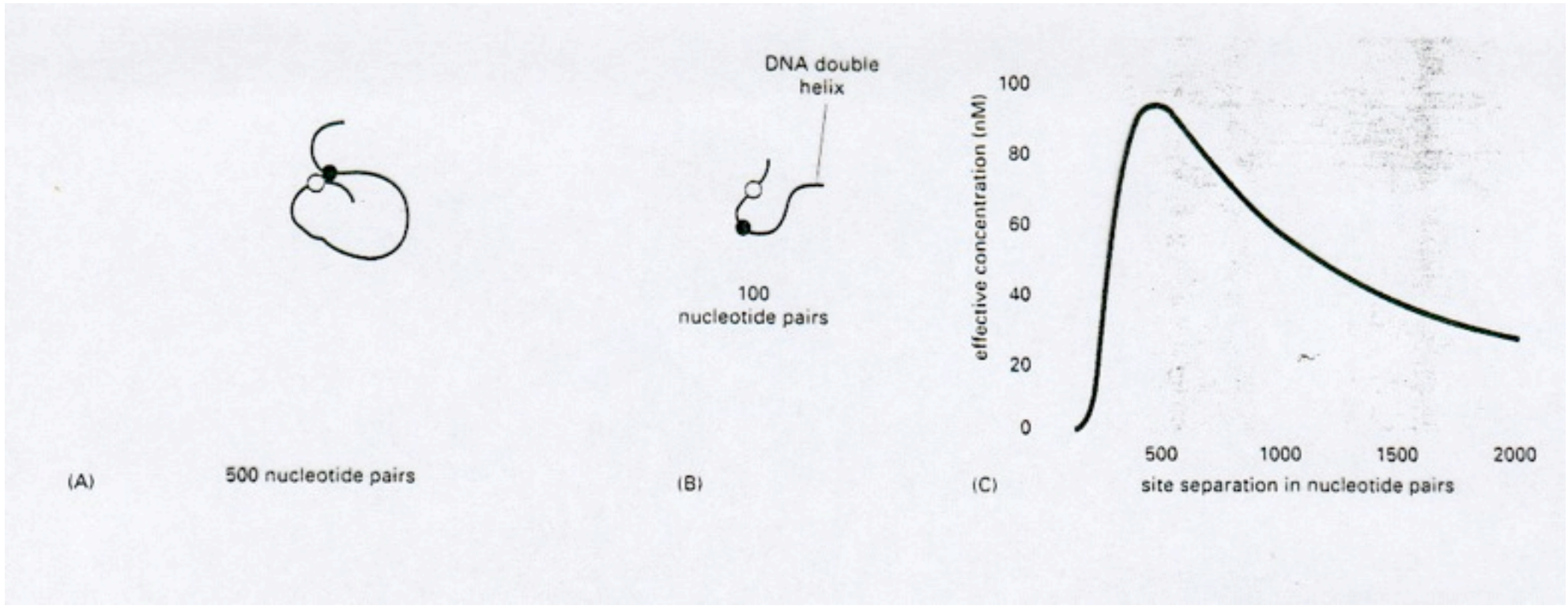
Activación transcripcional: factores transactivadores y elementos cis

- Acción a distancia
- Modulares (orientación y posición), distancias óptimas.
- Intercambiables: contexto independientes

Comportamiento teórico de elementos unidos a DNA: efecto de concentración efectiva



Brent & Ptashne, 1985

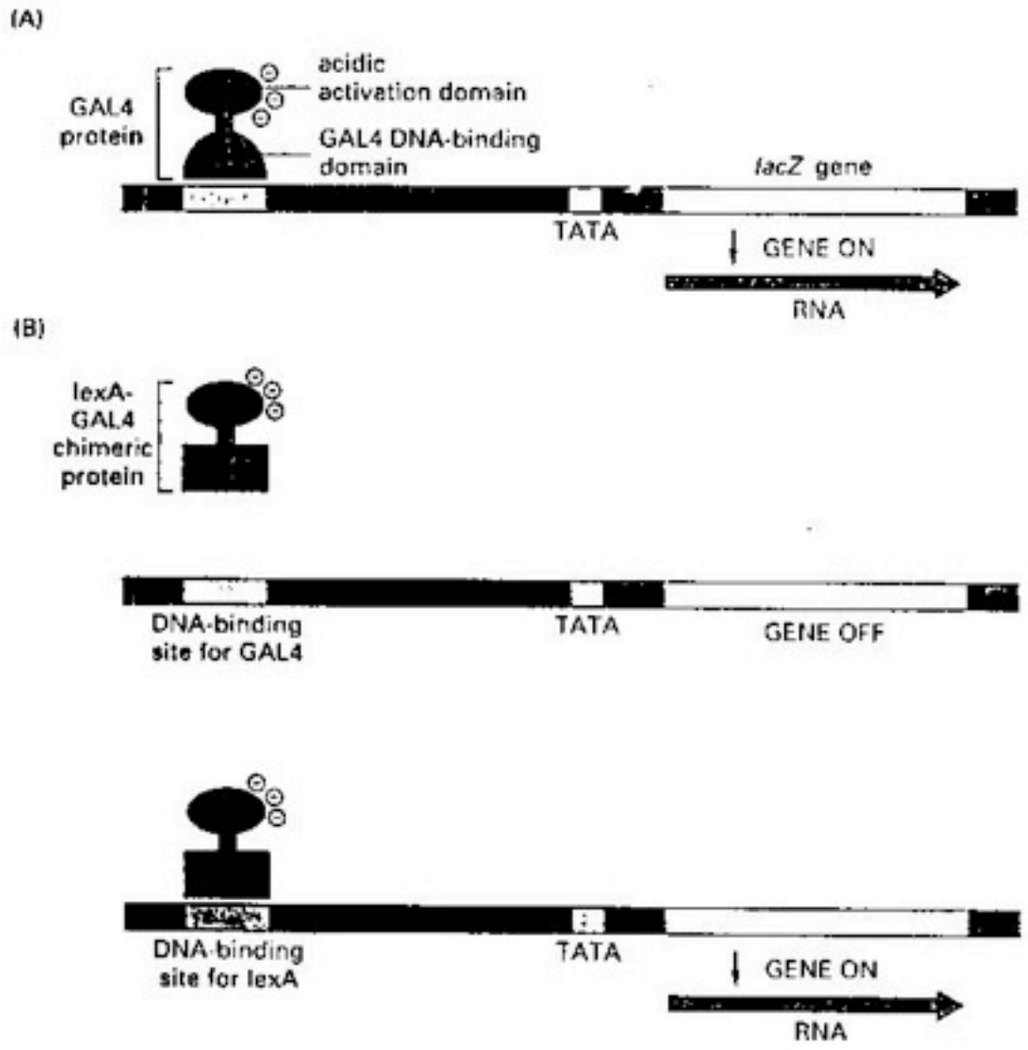


Figure 9–35 The modular structure of a gene activator protein. Outline of a domain-swap experiment that reveals the presence of independent DNA-binding and transcription-activating domains in the yeast gene activator protein GAL4. A functional activator can be reconstituted from the carboxyl-terminal portion of the GAL4 protein if it is attached to the DNA-binding domain of a bacterial gene regulatory protein (the lexA protein) by gene fusion techniques. When the resulting bacterial-yeast hybrid protein is produced in yeast cells, it will activate transcription from yeast genes provided that the specific DNA-binding site for the bacterial protein has been inserted next to them. (A) The normal activation of gene transcription produced by the GAL4 protein. (B) The chimeric gene regulatory protein requires the lexA-protein DNA-binding site for its activity.

GAL4 is normally responsible for activating the transcription of yeast genes that code for the enzymes that convert galactose to glucose. For the experiments shown here, the control region for one of these genes was fused to the *E. coli lacZ* gene, which codes for the enzyme β-galactosidase (see Figure 9–29). β-galactosidase is very simple to detect biochemically and thus provides a convenient way to monitor the expression level specified by a gene control region; *lacZ* thus serves as a *reporter gene* (see p. 321).

Factores transactivadores:

- Dominio unión a DNA
- Dominio activación
- Modulares

- Mecanismo de acción en eucariontes debe estar conservado por intercambiabilidad

- No hay necesidad de interacciones específicas ni cambios conformacionales como producto de las interacciones.

Experimento de "activator bypass" de Ptashne.

Cell, Vol. 81, 359–368, May 5, 1995, Copyright © 1995 by Cell Press

Contact with a Component of the Polymerase II Holoenzyme Suffices for Gene Activation

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Summary

In yeast strains bearing the point mutation called *GAL11P* (for potentiator), certain GAL4 derivatives lacking any classical activating region work as strong activators. The *P* mutation confers upon GAL11, a component of the RNA polymerase II holoenzyme, the ability to interact with a portion of the dimerization region of GAL4. The region of GAL11 affected by the *P* mutation is evidently functionally inert in ordinary cells, suggesting that this mutation is of no functional significance beyond creating an artificial target for the GAL4 dimerization fragment. From these observations and further analyses of GAL11, we propose that a single activator–holoenzyme contact can trigger gene activation simply by recruiting the latter to DNA.

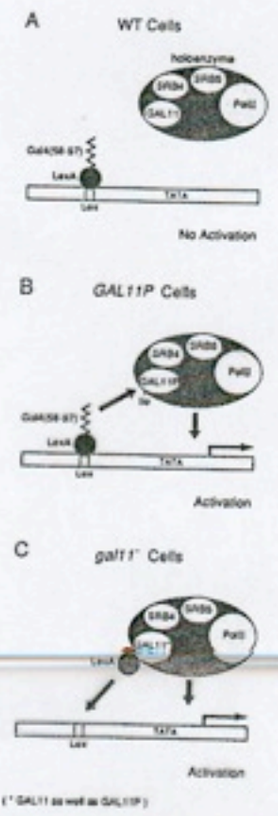

Figure 8. Potentiation by GAL11P and Activation by GAL11 Tethered to DNA

(A) A DNA-bound molecule fused to GAL4(58–97) does not activate transcription in *GAL11* wild-type cells. GAL11 and a subset of the other components that comprise RNA polymerase II holoenzyme are shown. Transcription factors TFIID and TFIIE, which are not part of the holoenzyme described by Koleske and Young (1994), are not shown.
(B) GAL4(58–97) works as an activating region in *GAL11P* cells because it specifically interacts with GAL11P and thereby recruits the RNA polymerase II holoenzyme complex to the promoter.
(C) A sequence-specific DNA-binding module fused to GAL11(or to GAL11P) recruits the holoenzyme to the promoter and activates transcription.

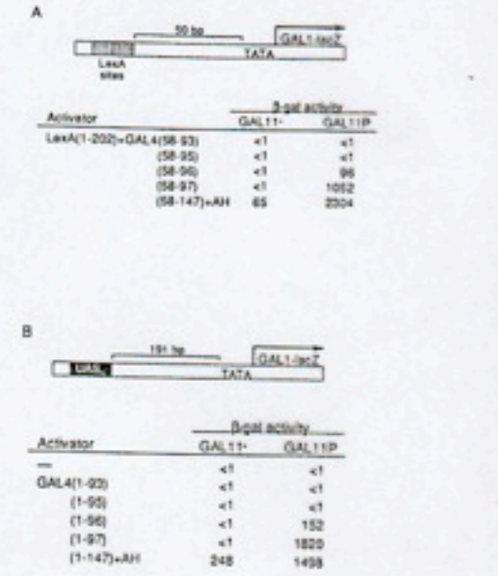

Figure 3. GAL4 Residues 58–97 Constitute an
GAL11P Cells

(A) GAL4(58–97) fused to LexA activates in GA
cated fusion proteins were expressed from the
low copy plasmid. GAL11 proteins were expres
promoter on low copy plasmids. The strain used i
is JPY42 and is *gal4*⁻ and *gal11*⁻. The integrated reporter template has two LexA-binding sites positioned 50 bp upstream of the *GAL1* TATA box.
(B) GAL4 residue 97 is the carboxyl border of the novel activating region. Deletion derivatives of GAL4 were expressed from the *ACT1* promoter on a low copy plasmid. *GAL11* alleles were those described in (A). The strain used in these experiments is JPY16 and is *gal4*⁻ and *gal11*⁻. The integrated reporter template has the UAS_G (an element that includes the GAL4-binding sites) at its native position upstream of the *GAL1* TATA box.
(C) Mutations in GAL4(58–97) impair the novel activating region. LexA(1–202)+GAL4(50–147)+AH, bearing either no mutations or the indicated amino acid substitutions, was expressed from the *ACT1* promoter on a low copy plasmid. *GAL11* alleles were those described in (A). The strain used in these experiments is JPY42.

Connecting a promoter-bound protein to TBP bypasses the need for a transcriptional activation domain

Sukalyan Chatterjee & Kevin Struhl*

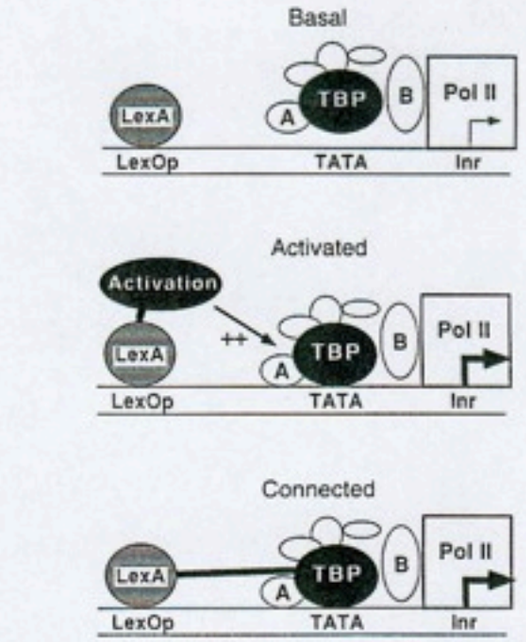

FIG. 2 Connecting a promoter-bound protein to TBP overrides the need for a transcriptional activation domain. Interactions of LexA hybrid proteins, TBP, TBP-associated factors (TAFs; shaded ovals), TFIIA, TFIIB and RNA polymease II at a promoter containing a LexA operator, TATA element and initiator (Inr). In basal transcription (LexA alone), the interaction between TBP and the TATA element is limiting (indicated by space between the two components), thereby leading to low levels of mRNA (thin arrow). Activation domains increase the recruitment or stability of TBP to the TATA element, thereby stimulating transcription (thick arrow). The target of the activation domain is not specified in the illustration (see text for discussion). A similar increase in transcription occurs when LexA is directly connected (thick line) to TBP. See text for details and limitations of this model.

Stimulation of RNA polymerase II transcription initiation by recruitment of TBP *in vivo*

Medio AT - requiere His 3 exp.

Natacha Klages & Michel Strubin

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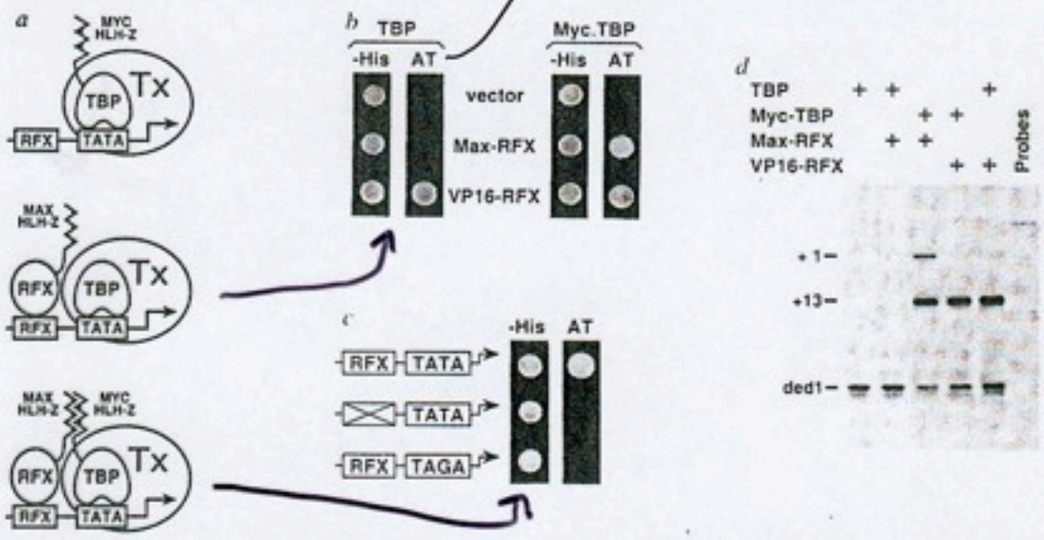


1 Recruitment of TBP to a target promoter stimulates RNA polymerase II transcription initiation *in vivo*. a, Schematic representation of strategy. MYC-HLH-Z and MAX-HLH-Z designate the helix-loop-helix-leucine-zipper dimerization motifs present in the human c-Myc oncoprotein and its partner Max, respectively[11]. Tx refers to the transcription machinery. b, Strains containing a *his3* allele with an upstream RFX-binding site and expressing the indicated TBP and RFX derivatives from plasmid DNAs were tested for growth on medium lacking histine (−His) containing 10 mM aminotriazole (AT). Growth on AT requires induced levels of *his3* expression. c, Effect of deletion of the RFX-binding site, insertion of a point mutation in the *his3* TATA-box (TAGA), on the ability of cells expressing Myc–TBP and Max–RFX to grow on 40 mM AT. d, Quantitation of his3 RNA levels by S1 nuclease analysis. Strains with the growth phenotype shown in b were analysed for *his3* (+1 and +13 transcripts) and *ded1* RNAs. The level of *ded1* RNA was used as an internal control.

METHODS. All the proteins are expressed from CEN-ARS vectors[20] under control of yeast TBP regulatory sequences[14]. The Myc dimerization motif derived from pVP-Myc73 (ref. 11) was fused to the N terminus of TBP molecule 4 (ref. 14). Max–RFX contains the *EcoRI–SalI* fragment from pVP-Max72 (ref. 11) fused to the *AgeI* site found in the RFX1 coding region[10]. VP16–RFX results from the fusion of the VP16 activation domain derived from pMSVP16 D1D3 (ref. 21) to the ATG initiator of RFX. The yeast strains, derived from KY320 (ref. 22), contain *his3* alleles with a single native or mutated RFX-binding site and 50 bp of random DNA inserted at the unique *EcoRI* site in *his3*–Δ94 carrying the relevant TATA elements[23]. Phenotypes were analysed by spotting 10^4 cells on minimal medium lacking histidine or containing AT. S1 nuclease protection experiments were done as described[24], except that the *ded1* radiolabelled oligonucleotide was diluted five-fold before hybridization.

Conclusiones del modelo de reclutamiento de Ptashne:

Los activadores poseen afinidad por algún componente de la maquinaria basal.

No se requiere un cambio conformacional de la maquinaria basal (o de RNA Pol II) para lograr la iniciación; basta reclutar los componentes.

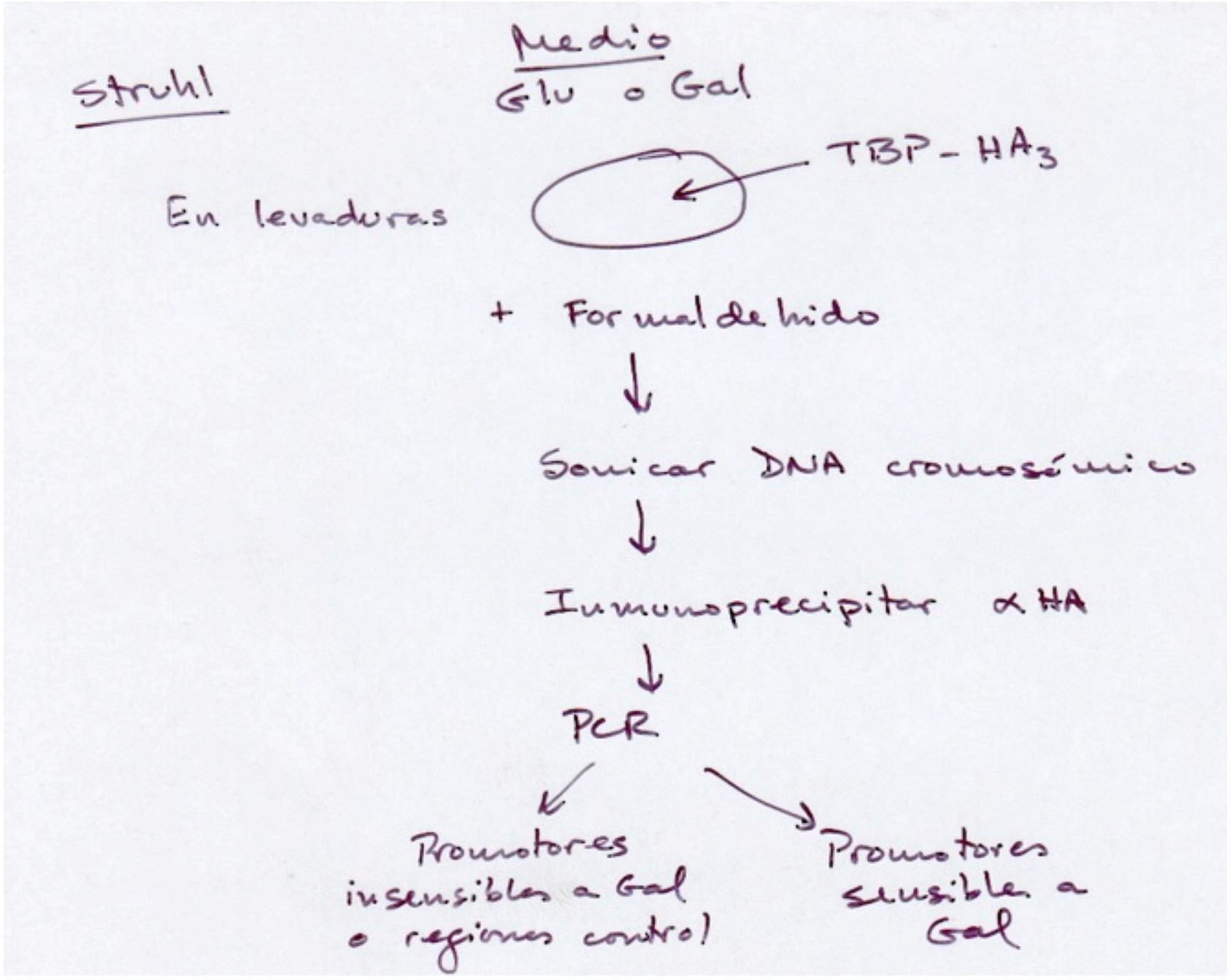
Las interacciones son arbitrarias y solo la fuerza de unión (energía) influye en el grado de activación.

Lo que ocurre *in vivo* es el aumento de la concentración de los activadores en la vecindad del promotor y el consiguiente aumento de la concentración de los componentes de la maquinaria basal.

La maquinaria basal (Pol II et al) no se une al promotor espontaneamente.

Efecto de "squelching".

Experimentos *in vivo* (Struhl y Green)



Li et al., 1999
Nature 399:605

Kuras & Struhl, 1999
Nature 399:609

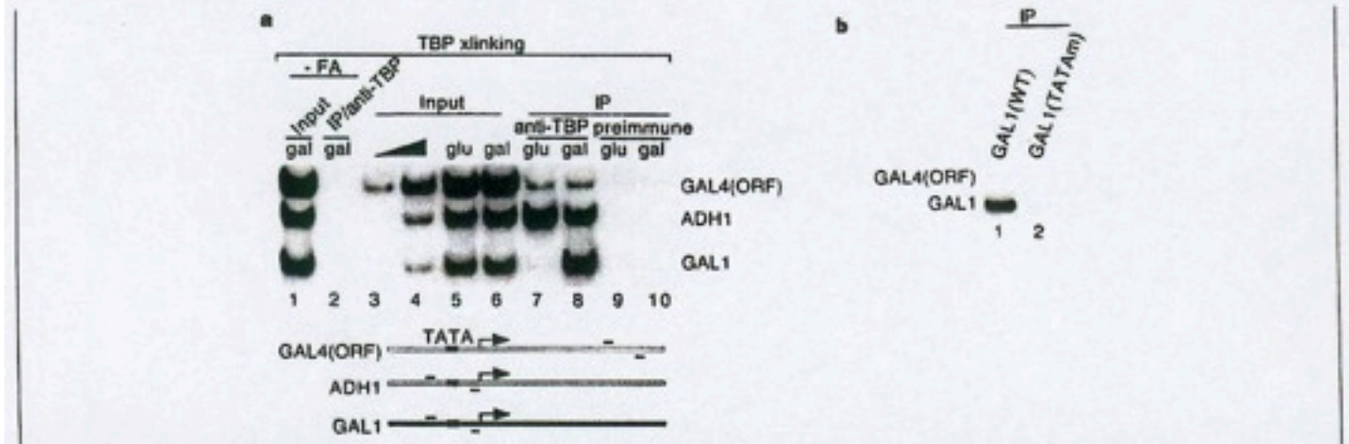
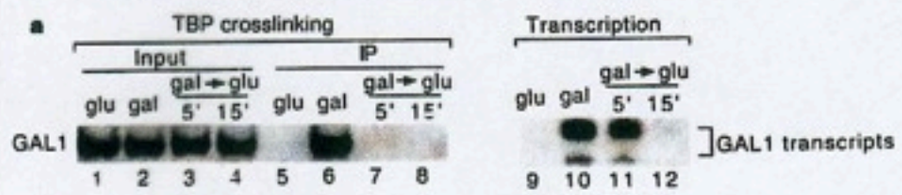


Figure 1 An *in vivo* crosslinking assay for measuring TBP-TATA-box interaction. **a**, *GAL1*, *ADH1*. The locations of the primers used for PCR amplification of the immunopurified DNA fragments are schematically shown. FA, formaldehyde. **b**, GAL1(TATAm). The crosslinking analysis was done using cells carrying a wild-type *GAL1* promoter (GAL1(WT)) or a *GAL1* promoter mutant containing a 3-bp substitution in the TATA-box sequence (GAL1(TATAm)) fused to the *lacZ* gene[4]. Cells were grown in YP plus 2% glycerol, 2% galactose and 2% acetate.



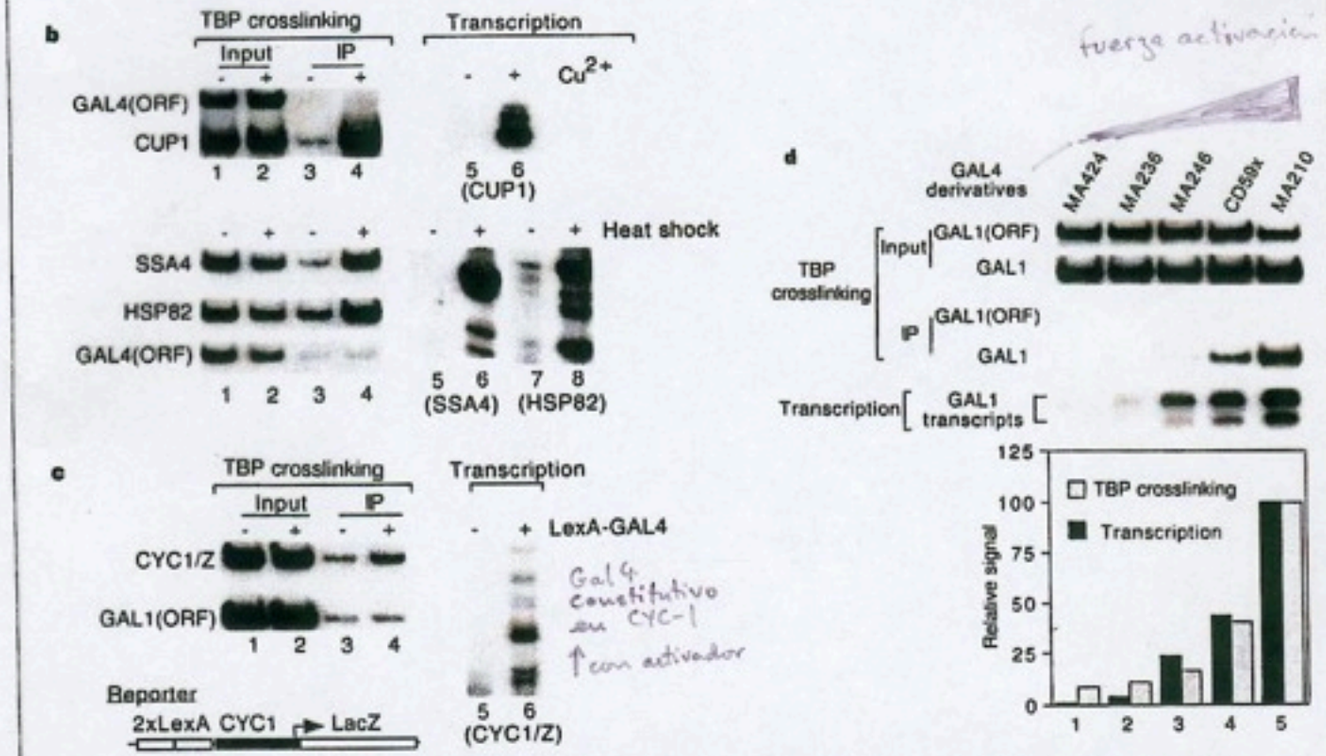


Figure 2 Correlation between TBP binding and transcriptional activity *in vivo*. **a**, *GAL1* transcriptional shut-off. TBP crosslinking was carried out at different times (0, 5, 10 min) after glucose (2%) was added to cells grown in galactose-containing medium. In parallel, cells were collected and total cellular RNA was prepared to analyse *GAL1* transcripts by primer extension. **b**, *CUP1*, *SSA4*, *HSP82*. To analyse the *CUP1* promoter, cells were grown in minimal complete medium and induced for 15 min by addition of $CuSO_4$ to a final concentration of 1 mM. For *SSA4* and *HSP82*, TBP-crosslinking was analysed immediately before or 15 min after cells were shifted to 39 °C. **c**, *CYC1*. Yeast transformants containing the reporter, pCTLx[3], and the LexA-GAL4 expression plasmid or control vector, were grown in minimal selective medium. TBP binding to the hybrid promoter was detected using a primer within the *CYC1* sequence and another at the junction of *CYC1-LacZ* fusion. The latter primer was also used in primer-extension analysis of the CYC1/Z transcripts. **d**, Activator series. GGY1 cells (*ga14*⁻ *gal80*⁻) transformed with plasmids expressing different GAL4-deletion derivatives[30] were grown in minimal selective medium containing 2% glycerol, 2% lactate and 2% galactose. TBP-crosslinking to the *GAL1* promoter and, as a control, to a sequence within the *GAL1* open reading frame (ORF) was analysed.

Conclusiones de los experimentos de ChIP:

•TBP es reclutado a la mayoría de los promotores

•Independientemente del promotor, el factor limitante en la activación transcripcional es la unión de TPB al promotor

•Como Pol II no se puede asociar al DNA sin TBP, los promotores inactivos carecen de este complejo

•La unión de TBP se ve favorecida o reforzada por componentes de la Pol II.

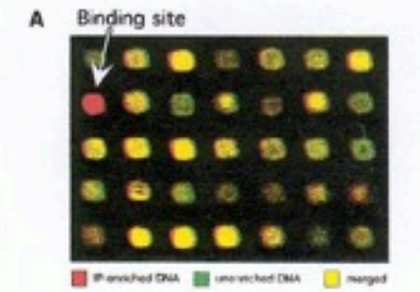
ChIp-CHIP

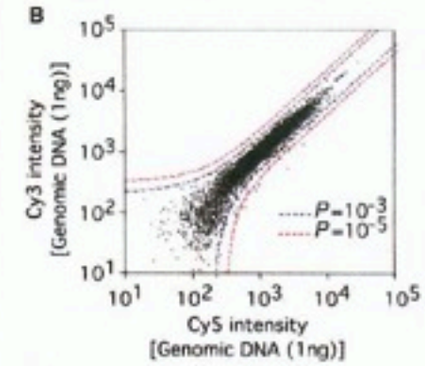
ChIp-Seq

ChIP...
en la era del genoma

Genome-Wide Location and Function of DNA Binding Proteins

Bing Ren,[1*] François Robert,[1*] John J. Wyrick,[1,2*] Oscar Aparicio,[2,4] Ezra G. Jennings,[1,2] Itamar Simon,[1] Julia Zeitlinger,[1] Jörg Schreiber,[1] Nancy Hannett,[1] Elenita Kanin,[1] Thomas L. Volkert,[1] Christopher J. Wilson,[5] Stephen P. Bell,[2,3] Richard A. Young[1,2†]





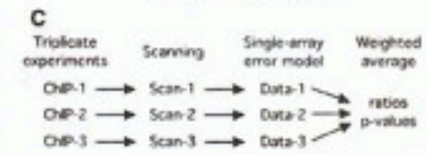
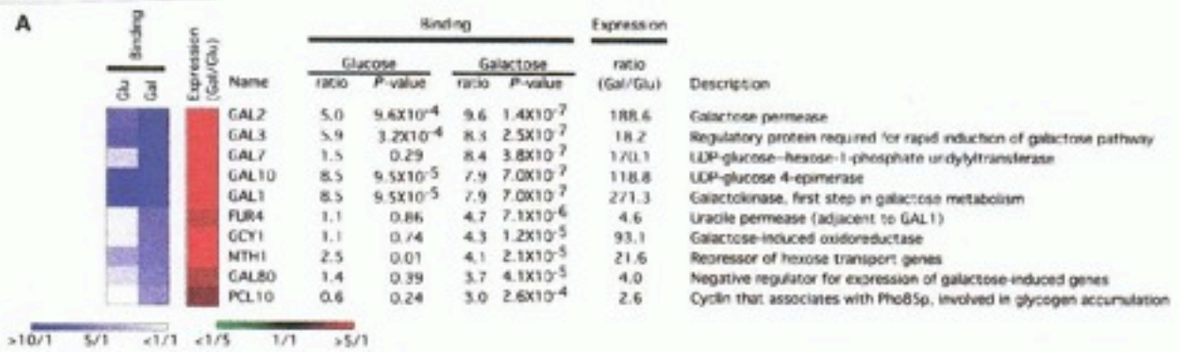
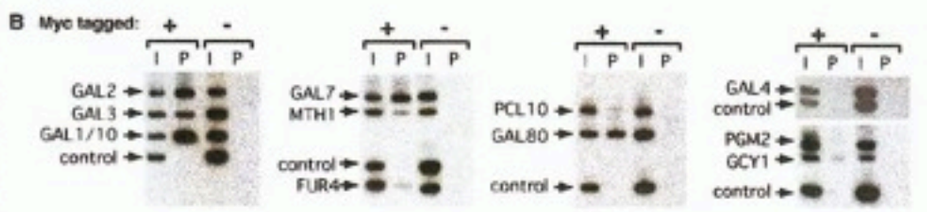
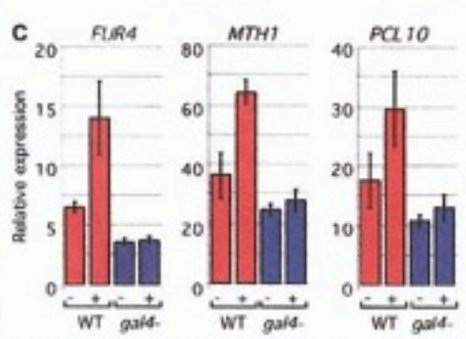


Fig. 1. The genome-wide location profiling method. (A) Close-up of a scanned image of a microarray containing DNA fragments representing 6361 intergenic regions of the yeast genome. The arrow points to a spot where the red intensity is over-represented, identifying a region bound in vivo by the protein under investigation. (B) Analysis of Cy3- and Cy5-labeled DNA amplified from 1 ng of yeast genomic DNA using a single-array error model (8). The error model cutoffs for *P* values equal to 10^{-3} and 10^{-5} are displayed. (C) Experimental design. For each factor, three independent experiments were performed and each of the three samples were analyzed individually using a single-array error model. The average binding ratio and associated *P* value from the triplicate experiments were calculated using a weighted average analysis method (6).



Name	Binding: Glucose ratio	Binding: Glucose *P*-value	Binding: Galactose ratio	Binding: Galactose *P*-value	Expression ratio (Gal/Glu)	Description
GAL2	5.0	$9.6X10^{-4}$	9.6	$1.4X10^{-7}$	188.6	Galactose permease
GAL3	5.9	$3.2X10^{-4}$	8.5	$2.5X10^{-7}$	18.2	Regulatory protein required for rapid induction of galactose pathway
GAL7	1.5	0.29	8.4	$3.8X10^{-7}$	170.1	UDP-glucose–hexose-1-phosphate uridylyltransferase
GAL10	8.5	$9.5X10^{-5}$	7.9	$7.0X10^{-7}$	118.8	UDP-glucose 4-epimerase
GAL1	8.5	$9.5X10^{-5}$	7.9	$7.0X10^{-7}$	271.3	Galactokinase, first step in galactose metabolism
FUR4	1.1	0.86	4.7	$7.1X10^{-6}$	4.6	Uracil permease (adjacent to GAL1)
GCY1	1.1	0.74	4.3	$1.2X10^{-5}$	93.1	Galactose-induced oxidoreductase
MTH1	2.5	0.01	4.1	$2.1X10^{-5}$	21.6	Repressor of hexose transport genes
GAL80	1.4	0.39	3.7	$4.1X10^{-5}$	4.0	Negative regulator for expression of galactose-induced genes
PCL10	0.6	0.24	3.0	$2.6X10^{-4}$	2.6	Cyclin that associates with Pho85p, involved in glycogen accumulation





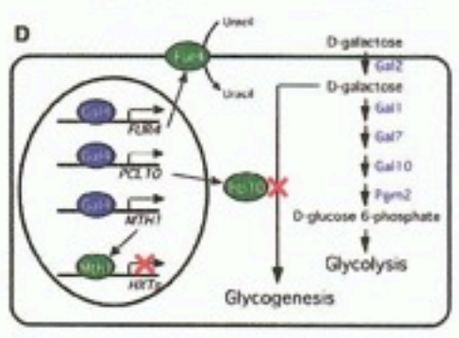


Fig. 2. Genome-wide location of Gal4 protein. (A) Genes whose promoter regions were bound by myc-tagged Gal4 (*P* value < 0.001) and whose expression levels were induced at least twofold by galactose are listed. The weight-averaged ratios and *P* values are shown for Gal4 binding in galactose and glucose. Binding ratios are also displayed using a blue and white color scheme and expression ratios of galactose/glucose are displayed using a red and green color scheme. (B) Confirmation of microarray data for each gene in panel A using conventional chromatin IP procedure. Strains with (+) or without (–) a myc-tagged Gal4 protein were grown in galactose. Amplification of the unenriched DNA (I) and IP-enriched DNA (P) is shown. *ARN1* (control) was used as a negative control. (C) Galactose-induced expression of *FUR4*, *MTH1*, and *PCL10* is Gal4-dependent. Samples from wild-type and gal4– strains were taken before and after addition of galactose. The expression of *FUR4*, *MTH1*, and *PCL10* was monitored by quantitative reverse transcriptase–PCR (RT-PCR) and was quantified by phosphorimaging. (D) Model summarizing the role of Gal4 in galactose-dependent cellular regulation. The products of genes newly identified as directly regulated by Gal4 are shown as green circles; those previously identified are shown in blue.

In vitro:

1º	2º	Tx
Histonas	GTFs	+
GTFs	Histonas	+++++

- **La activación transcripcional en eucariontes requiere mas pasos que el simple reclutamiento.**

- **Aunque el estado basal es represivo, existen muchos mecanismos de represión específicos.**

Cell, Vol. 98, 1–4, July 9, 1999, Copyright ©1999 by Cell Press

Fundamentally Different Logic of Gene Regulation in Eukaryotes and Prokaryotes

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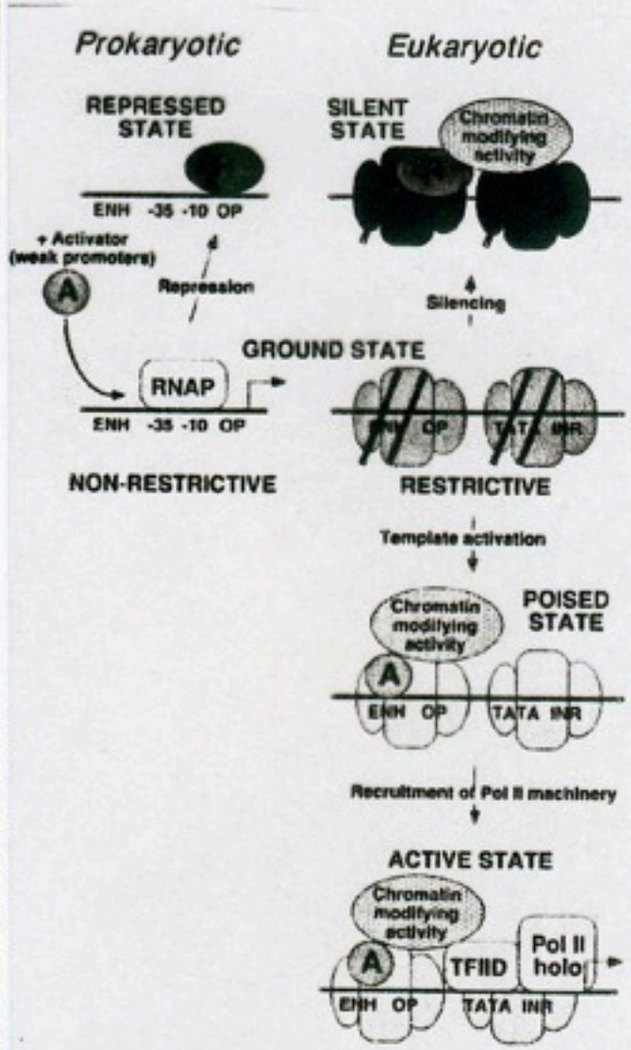


Figure 1. Transcriptional States in Prokaryotes and Eukaryotes

Activators (A) and repressors (R) interact respectively with enhancer (ENH) or operator (OP) sequences and affect transcription by prokaryotic RNA polymerase (RNAP) or the eukaryotic Pol II machinery (TFIID + Pol II holoenzyme). In eukaryotes, recruitment of chromatin modifying activities by activators or repressors leads to altered chromatin structure (depicted by color or DNA within nucleosomes). See text for details.

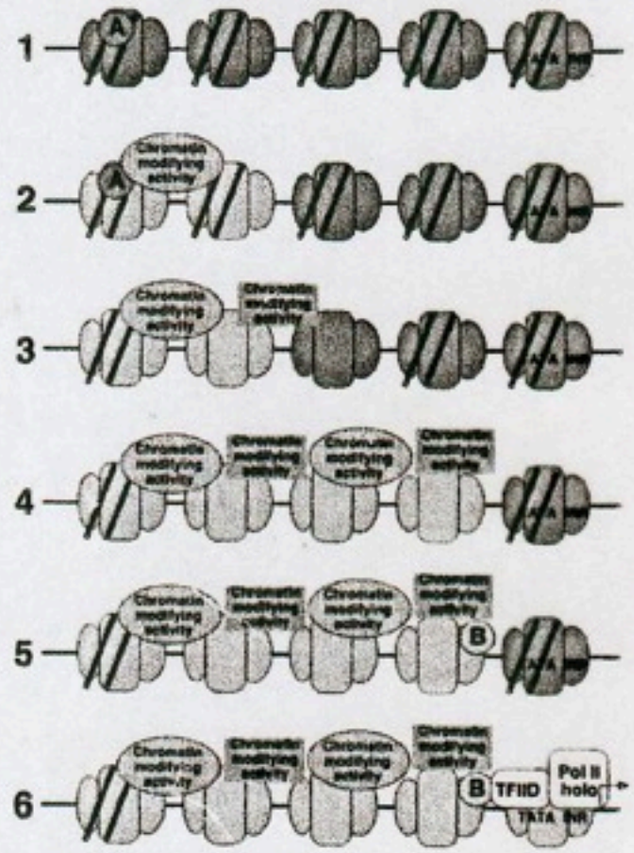


Figure 2. Hypothetical Intermediate States of Eukaryotic Transcription for a Given Promoter

Activator A binds to unmodified nucleosomal templates, leading to successive recruitment of chromatin modifying activities and the creation of an extended domain of active chromatin structure that permits binding of activator B and subsequent recruitment of the Pol II machinery. Binding of activator A is transient, but the recruited chromatin modifying activities remain stably associated for extended times. The existence, order, and stability of the indicated states can be developmentally regulated, but will vary according to the specific promoter.

Activación y Represión transcripcional por acceso a cromatina

Activación y Represión transcripcional por acceso a cromatina

1. Regulación por modificaciones a la cromatina:
metilación (DNA e histonas) y acetilación de histonas (HATs yHDACs).

Activación y Represión transcripcional por acceso a cromatina

1. Regulación por modificaciones a la cromatina:
metilación (DNA e histonas) y acetilación de histonas (HATs yHDACs).

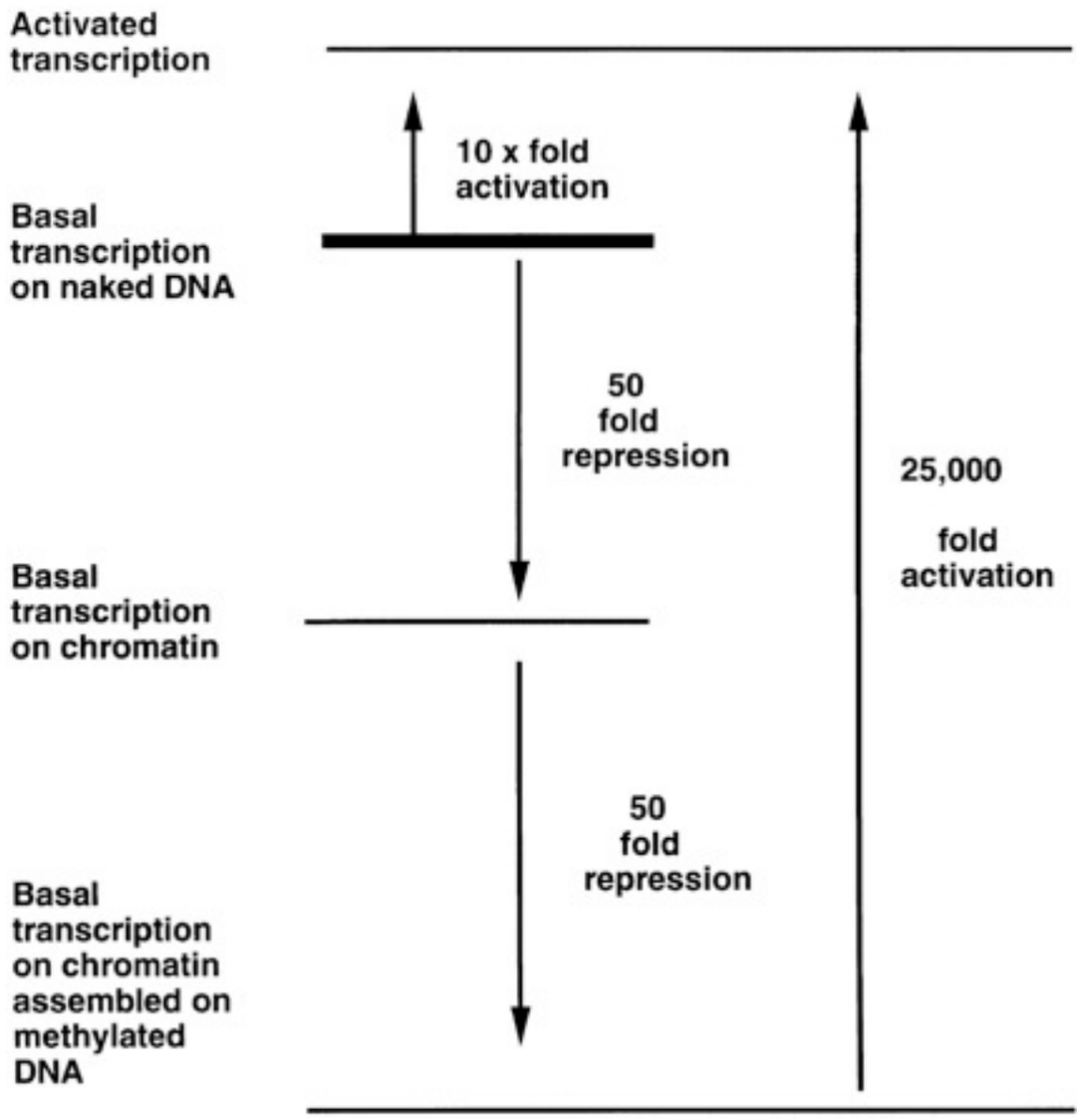
2. Regulación por remodelamiento de la cromatina

Activación y Represión transcripcional por acceso a cromatina

1. Regulación por modificaciones a la cromatina:
metilación (DNA e histonas) y acetilación de histonas (HATs yHDACs).

Activación y Represión transcripcional por acceso a cromatina

1. Regulación por modificaciones a la cromatina:
metilación (DNA e histonas) y acetilación de histonas (HATs yHDACs).



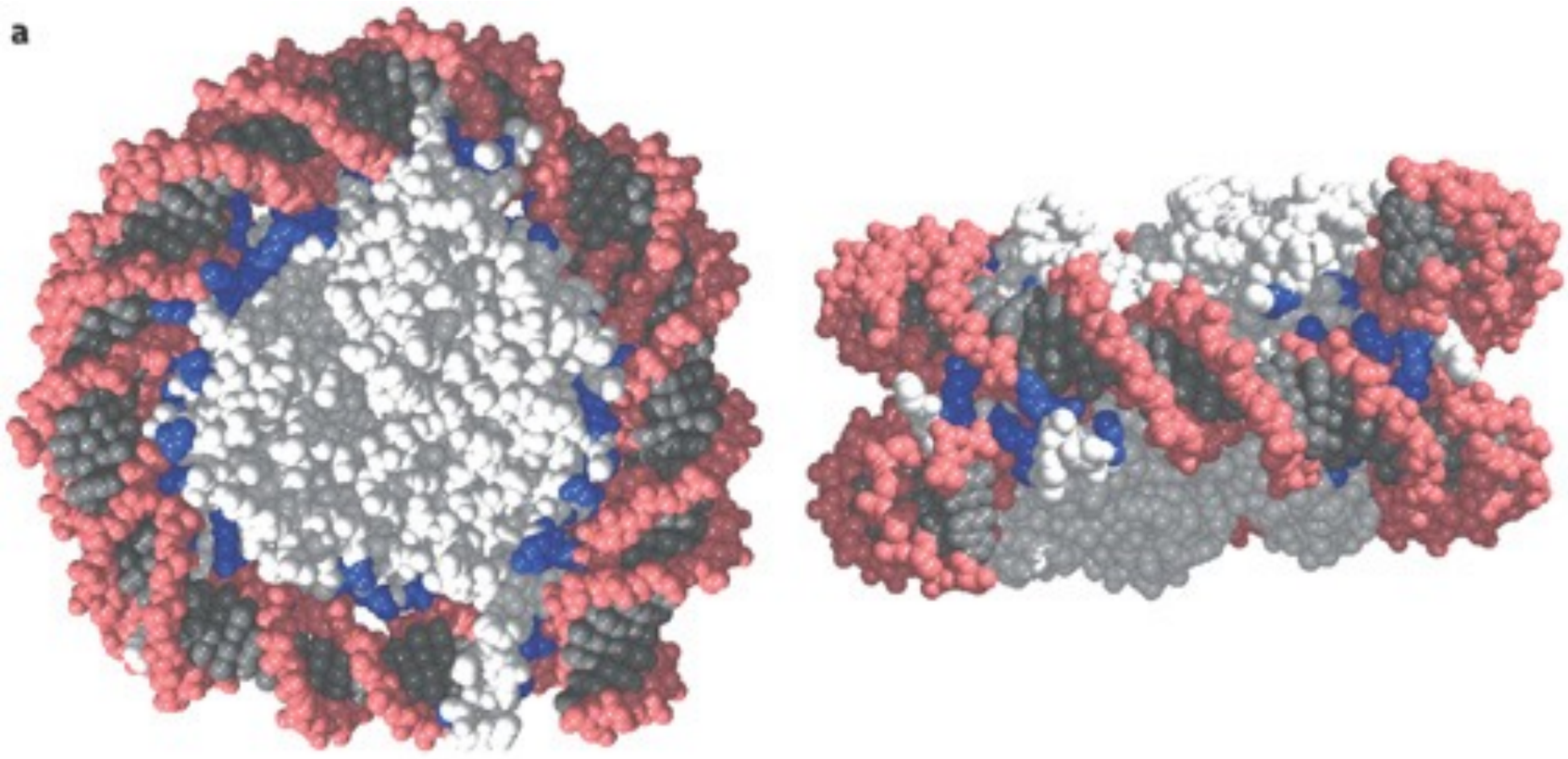
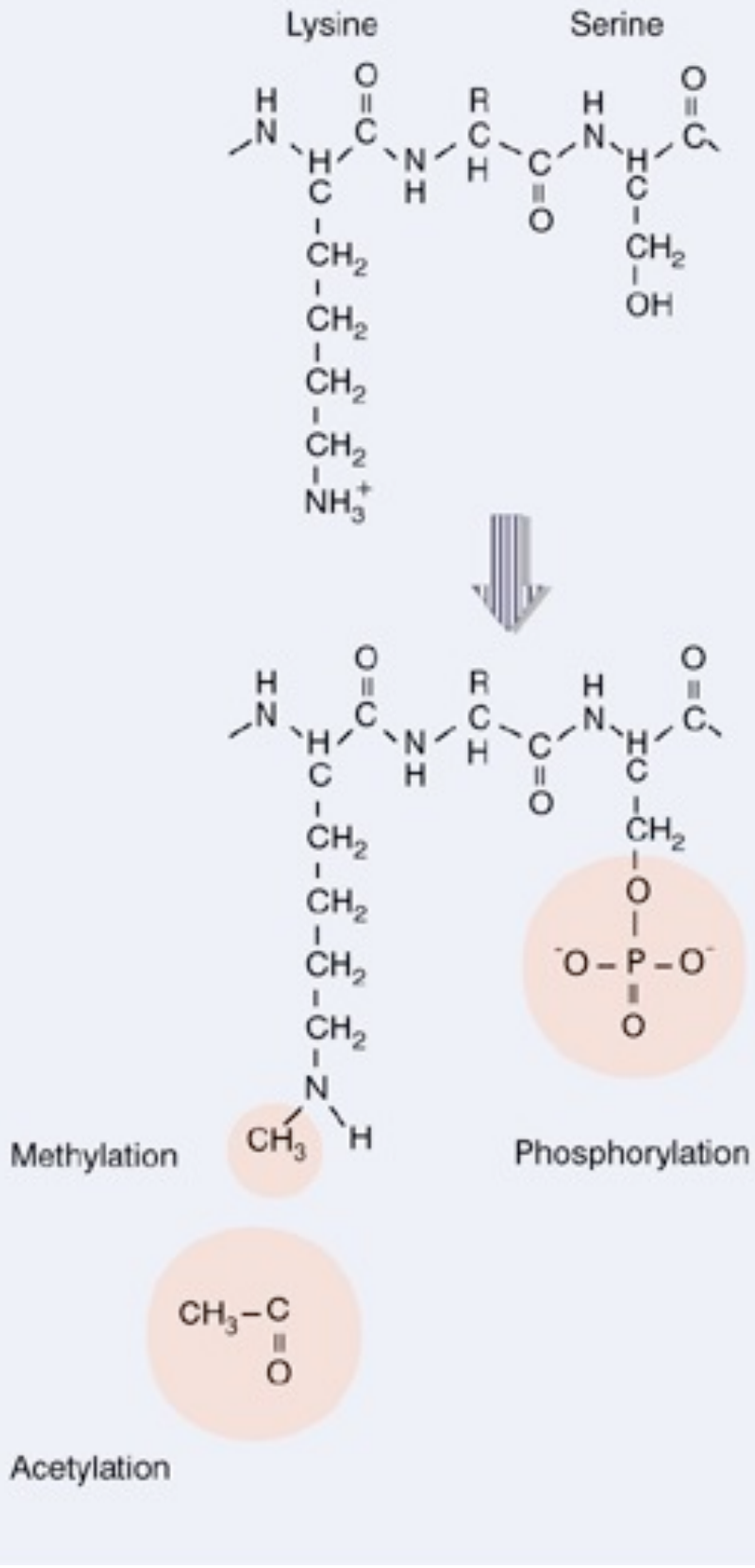
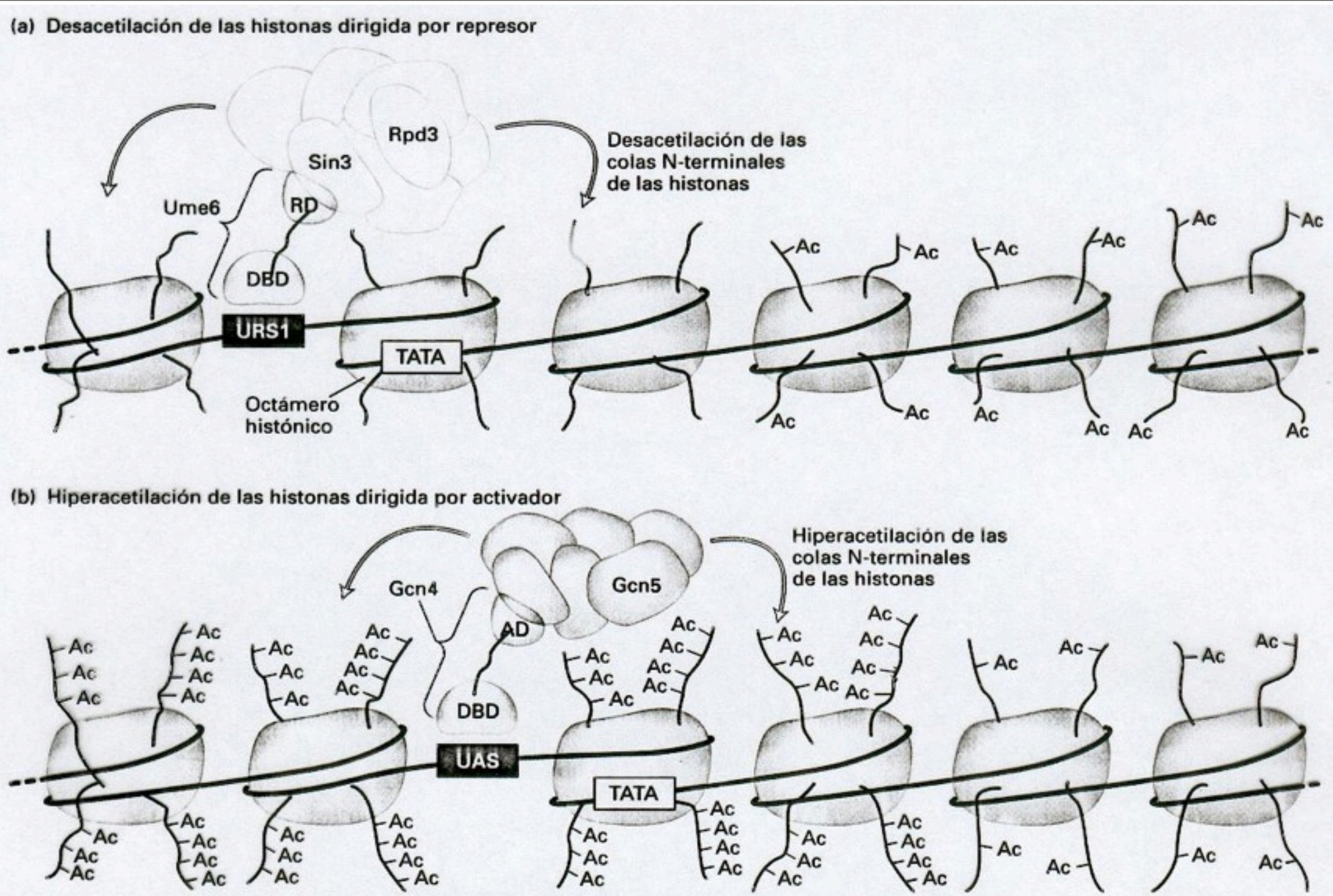


Figure 1 | **Nucleosome structure. a** | Structure of a nucleosome core particle (front and side view)[2,131]. Histones are shown in light grey, and the DNA helix is shown in dark grey with a pink backbone. Basic amino acids (lysine and arginine) within 7 Å of the DNA are shown in blue to emphasize the electrostatic contacts between the DNA phosphates and the histones. **b** | A schematic of DNA wrapped around a nucleosome. Examples of histone tail modifications (Ac, acetylation; Me, methylation) and histone variants (H2A.Z and H3.3) are shown. Arrows indicate the replacement of canonical histones with histone variants. Part **a** courtesy of S. Tan, Pennsylvania State University, USA.

Modificaciones de histonas

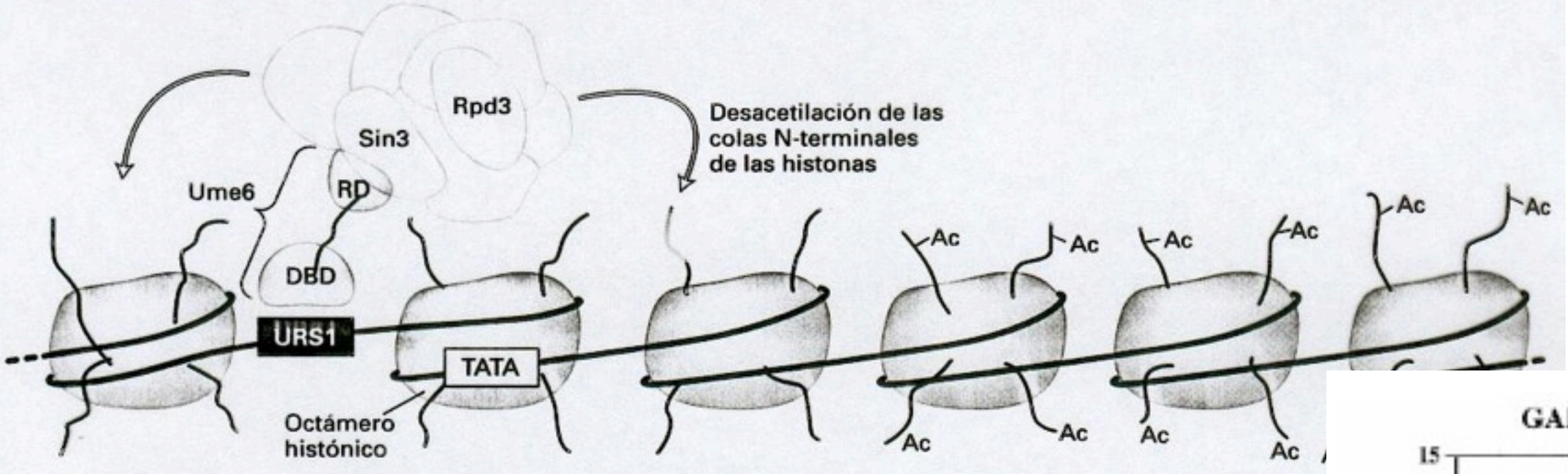
Figure 19.25 Acetylation of lysine or phosphorylation of serine reduces the overall positive charge of a protein.



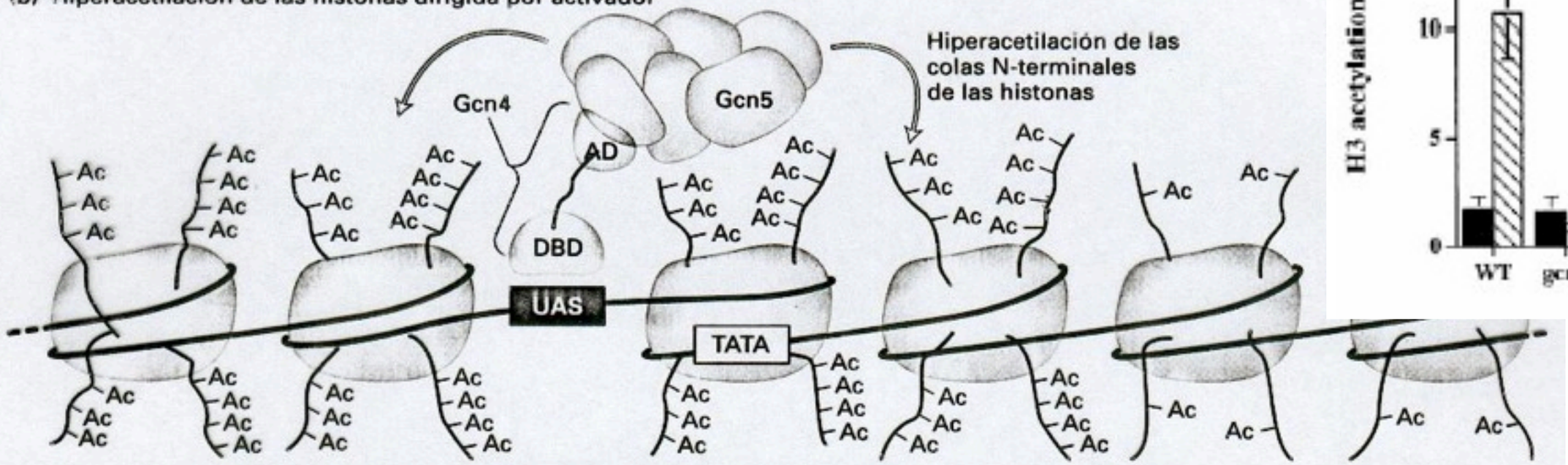


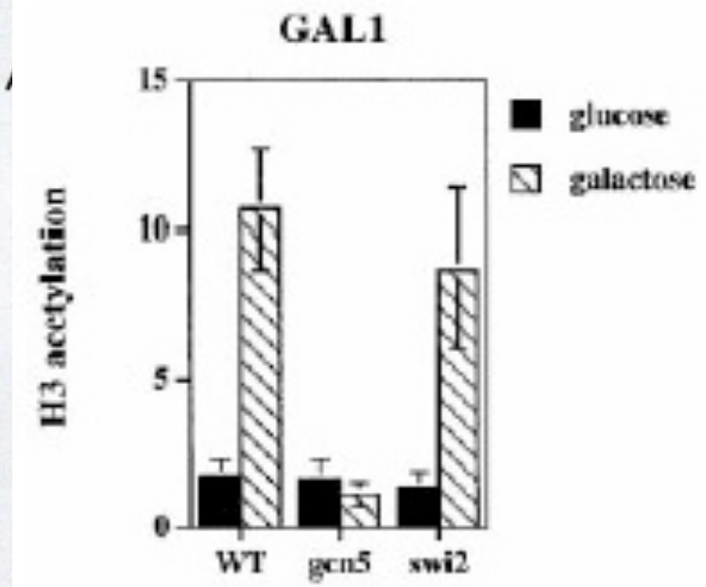
▲ **Fig. 10-58. Papel de la desacetilación y la hiperacetilación de las colas N-terminales de las histonas en el control de la transcripción en las levaduras.** (a) Desacetilación de las colas N-terminales de las histonas dirigida por represor. El dominio de fijación al DNA (DBD) del represor Ume6 interactúa con un elemento de control hacia 5′ específico (URS1) de los genes que regula. El dominio de represión de Ume6 fija Sin3, una subunidad de un complejo multiproteico que incluye la histona desacetilasa Rpd3. La desacetilación de colas N-terminales histónicas, en los nucleosomas de la región del sitio de unión del Ume6, inhibe la fijación de factores de transcripción generales a la caja TATA, con lo cual se reprime la expresión génica. (b) Hiperacetilación de las colas N-terminales de las histonas dirigida por activador. El dominio de fijación al DNA de la Gcn4 interactúa con secuencias activadoras hacia 5′ (UAS) específicas de los genes que regula. El dominio de activación (AD) de la Gcn4 interactúa entonces con un complejo multiproteico de histona acetilasa que incluye la subunidad catalítica Gcn5. La ulterior hiperacetilación de las colas N-terminales de las histonas en los nucleosomas cercanos al sitio de fijación para la Gcn4 facilita el acceso de los factores de transcripción generales necesarios para la iniciación. La represión y activación de algunos genes en los eucariontes superiores se produce por mecanismos similares.

(a) Desacetilación de las histonas dirigida por represor



(b) Hiperacetilación de las histonas dirigida por activador





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▲ **Fig. 10-58. Papel de la desacetilación y la hiperacetilación de las colas N-terminales de las histonas en el control de la transcripción en las levaduras.** (a) Desacetilación de las colas N-terminales de las histonas dirigida por represor. El dominio de fijación al DNA (DBD) del represor Ume6 interactúa con un elemento de control hacia 5' específico (URS1) de los genes que regula. El dominio de represión de Ume6 fija Sin3, una subunidad de un complejo multiproteico que incluye la histona desacetilasa Rpd3. La desacetilación de colas N-terminales histónicas, en los nucleosomas de la región del sitio de unión del Ume6, inhibe la fijación de factores de transcripción generales a la caja TATA, con lo cual se reprime la expresión génica. (b) Hiperacetilación de las colas N-terminales de las histonas dirigida por activador. El dominio de fijación al DNA de la Gcn4 interactúa con secuencias activadoras hacia 5' (UAS) específicas de los genes que regula. El dominio de activación (AD) de la Gcn4 interactúa entonces con un complejo multiproteico de histona acetilasa que incluye la subunidad catalítica Gcn5. La ulterior hiperacetilación de las colas N-terminales de las histonas en los nucleosomas cercanos al sitio de fijación para la Gcn4 facilita el acceso de los factores de transcripción generales necesarios para la iniciación. La represión y activación de algunos genes en los eucariontes superiores se produce por mecanismos similares.

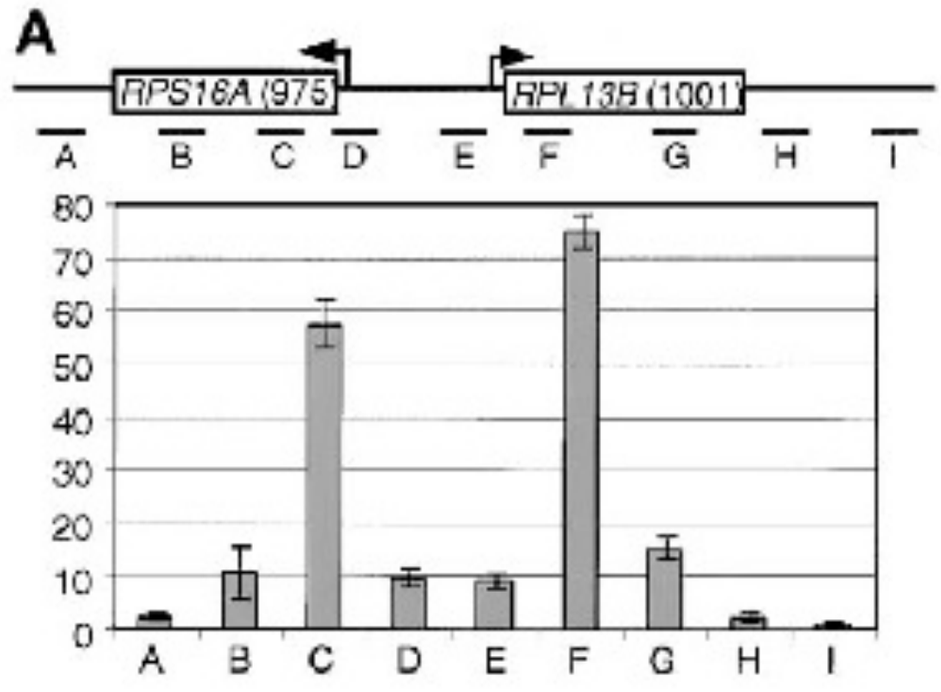
Metilación de Histonas

Molecular Cell, Vol. 11, 709–719, March, 2003, Copyright ©2003 by Cell Press

Targeted Recruitment of Set1 Histone Methylase by Elongating Pol II Provides a Localized Mark and Memory of Recent Transcriptional Activity

Huck Hui Ng,[1,4] François Robert,[2,4]
Richard A. Young,[2,3] and Kevin Struhl[1,*]

et al., 2002) or to repressor binding sites (
2002; Czermin et al., 2002; Kuzmichev et al., 2



Set1: metila en K4 de H3

<u>Cromatina activa:</u>
metilación en lisinas K4, K36 y K79 de H3.

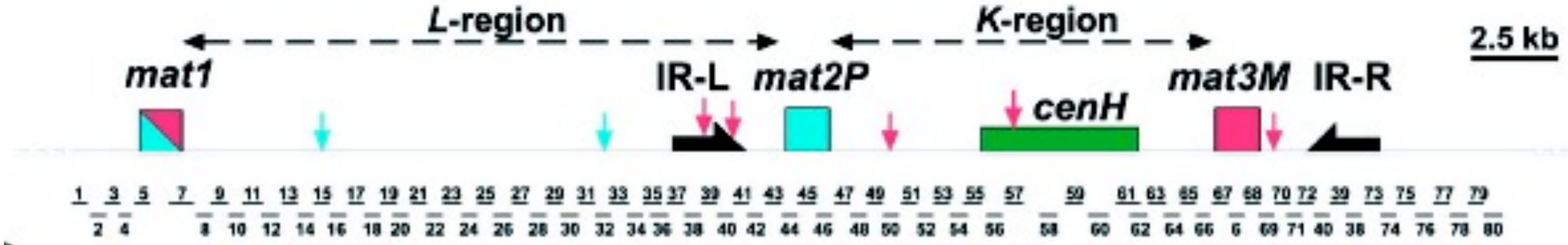
<u>Cromatina reprimida:</u>
metilación en lisinas K9 y K27 de la H3 o K20 de la H4.

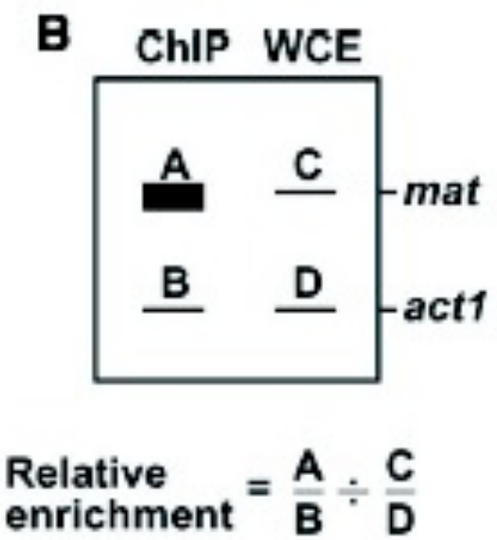
Transitions in Distinct Histone H3 Methylation Patterns at the Heterochromatin Domain Boundaries

10 AUGUST 2001 VOL 293 SCIENCE

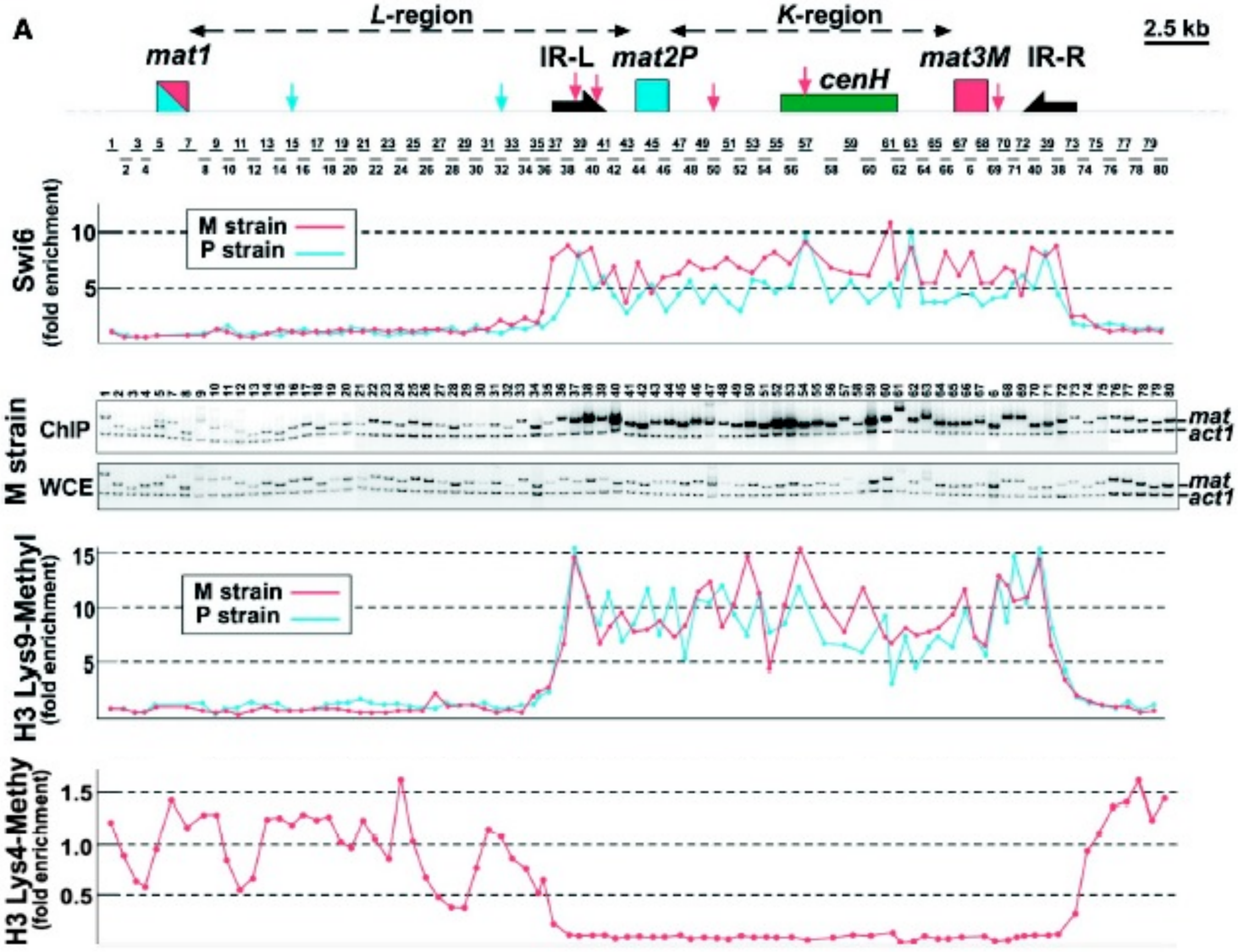
Ken-ichi Noma,[1] C. David Allis,[2] Shiv I. S. Grewal[1]*

Expresión de transgenes:
azul: activos
rojo: inactivos





ChIP con:
-anti-H3 metilada K4 y K9
-Swi6, proteína involucrada en transición a heterocromatina

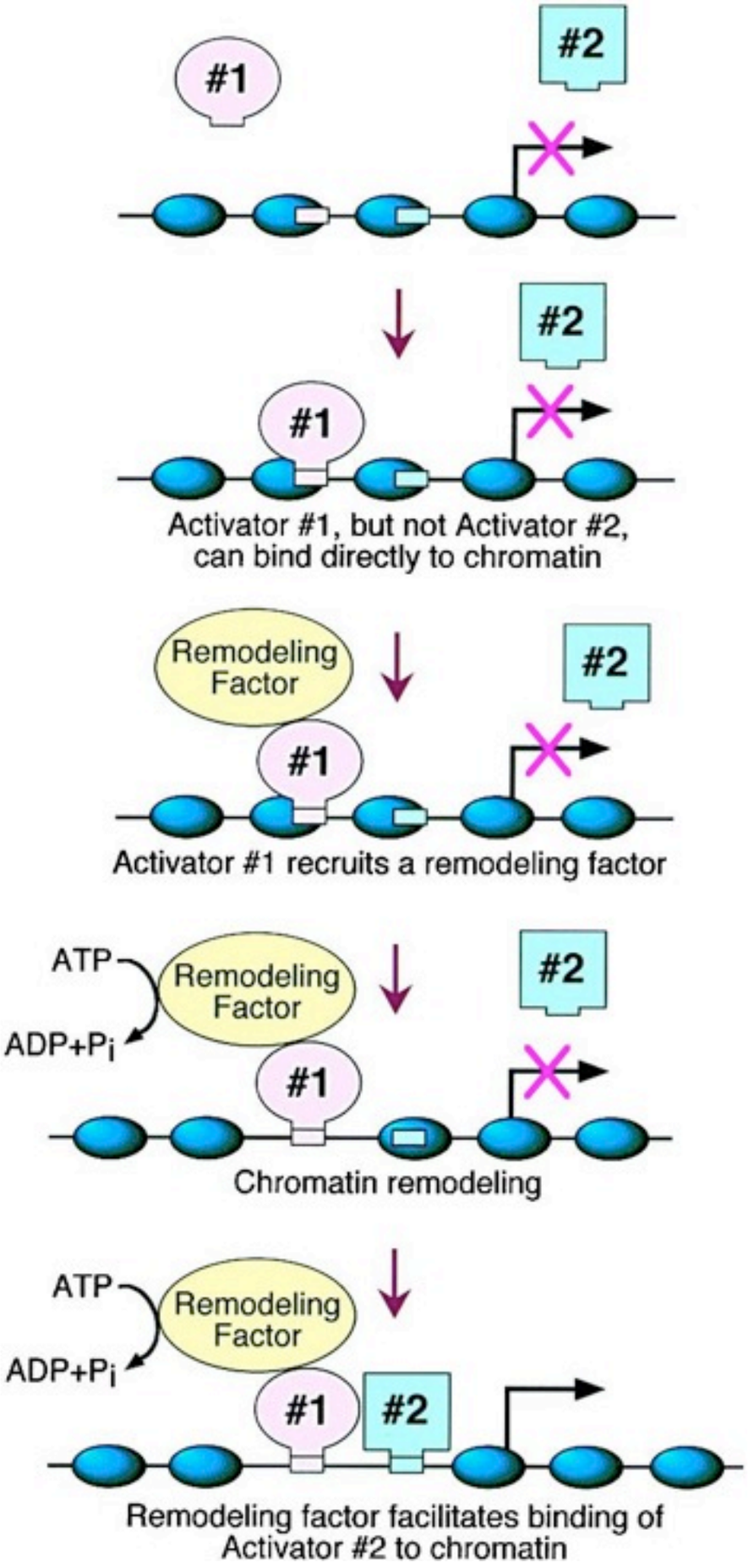

A
L-region
K-region
2.5 kb
mat1
IR-L
mat2P
cenH
mat3M
IR-R
Swi6
(fold enrichment)
M strain
P strain
M strain
ChIP
WCE
mat
act1
H3 Lys9-Methyl
(fold enrichment)
H3 Lys4-Methy
(fold enrichment)

La remodelación es un paso previo a la activación de la maquinaria basal.

<u>Preguntas</u>:

¿Cómo se regula la activación transcripcional *in vivo*?

¿Porqué son necesarios todos estos pasos?

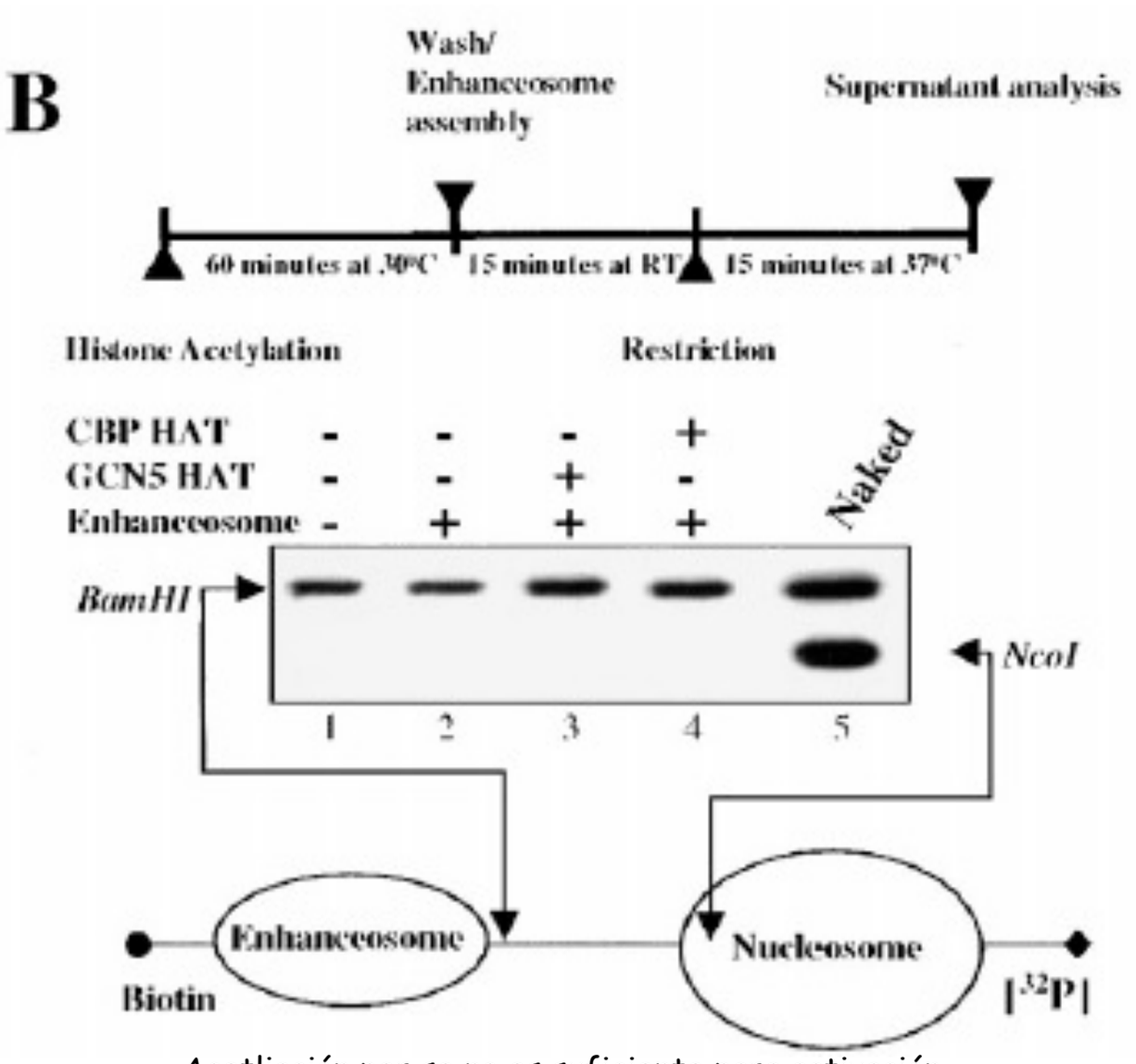


Cell, Vol. 103, 667–678, November 10, 2000, Copyright ©2000 by Cell Press

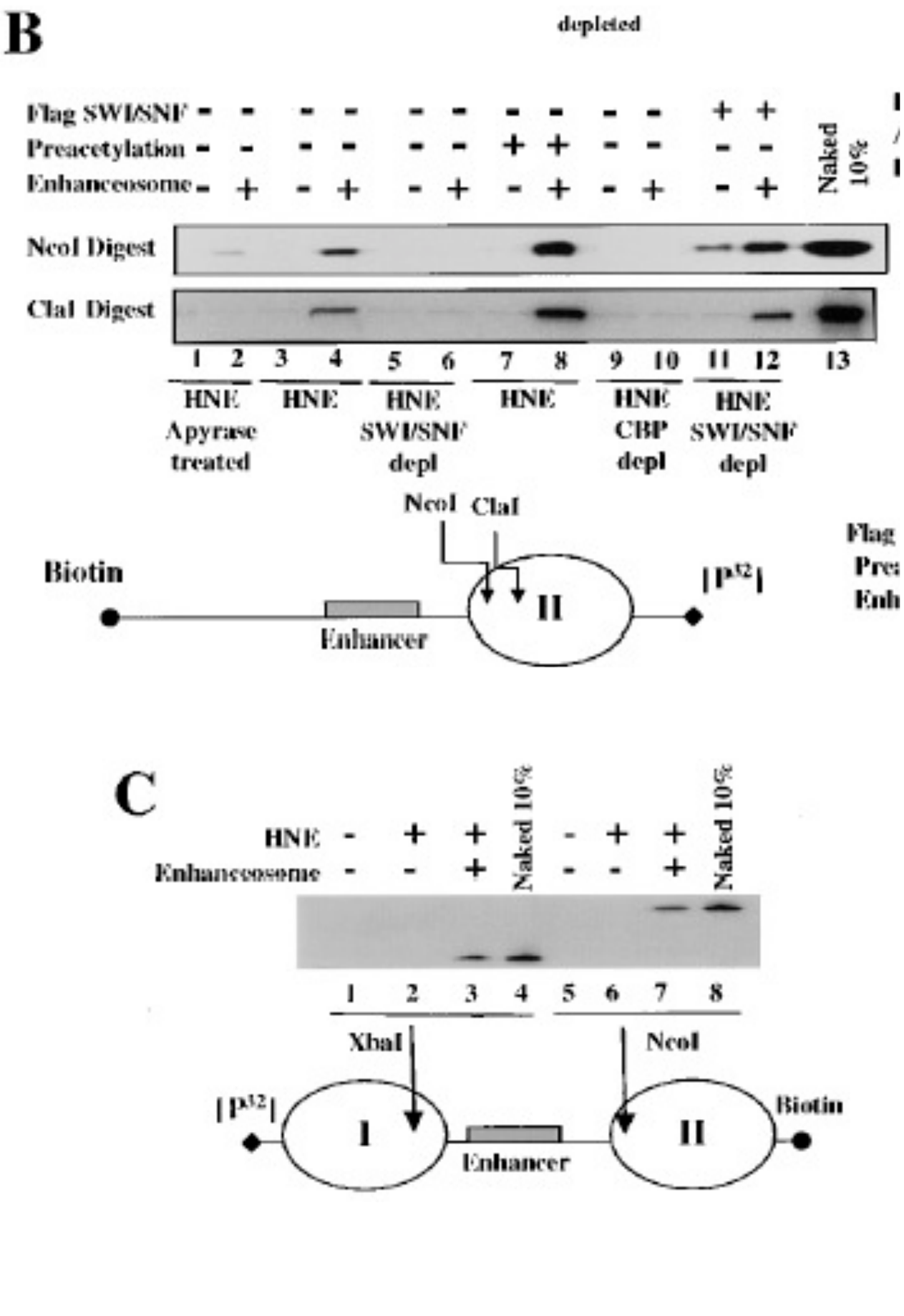
Ordered Recruitment of Chromatin Modifying and General Transcription Factors to the IFN-β Promoter

Theodora Agalioti,*§ Stavros Lomvardas,*§ Bhavin Parekh,† Junming Yie,* Tom Maniatis,† and Dimitris Thanos*‡

are multi-subunit assemblies of eigh
tides in which the DNA-dependent A
BRG1 or the BRM1 proteins. Chr

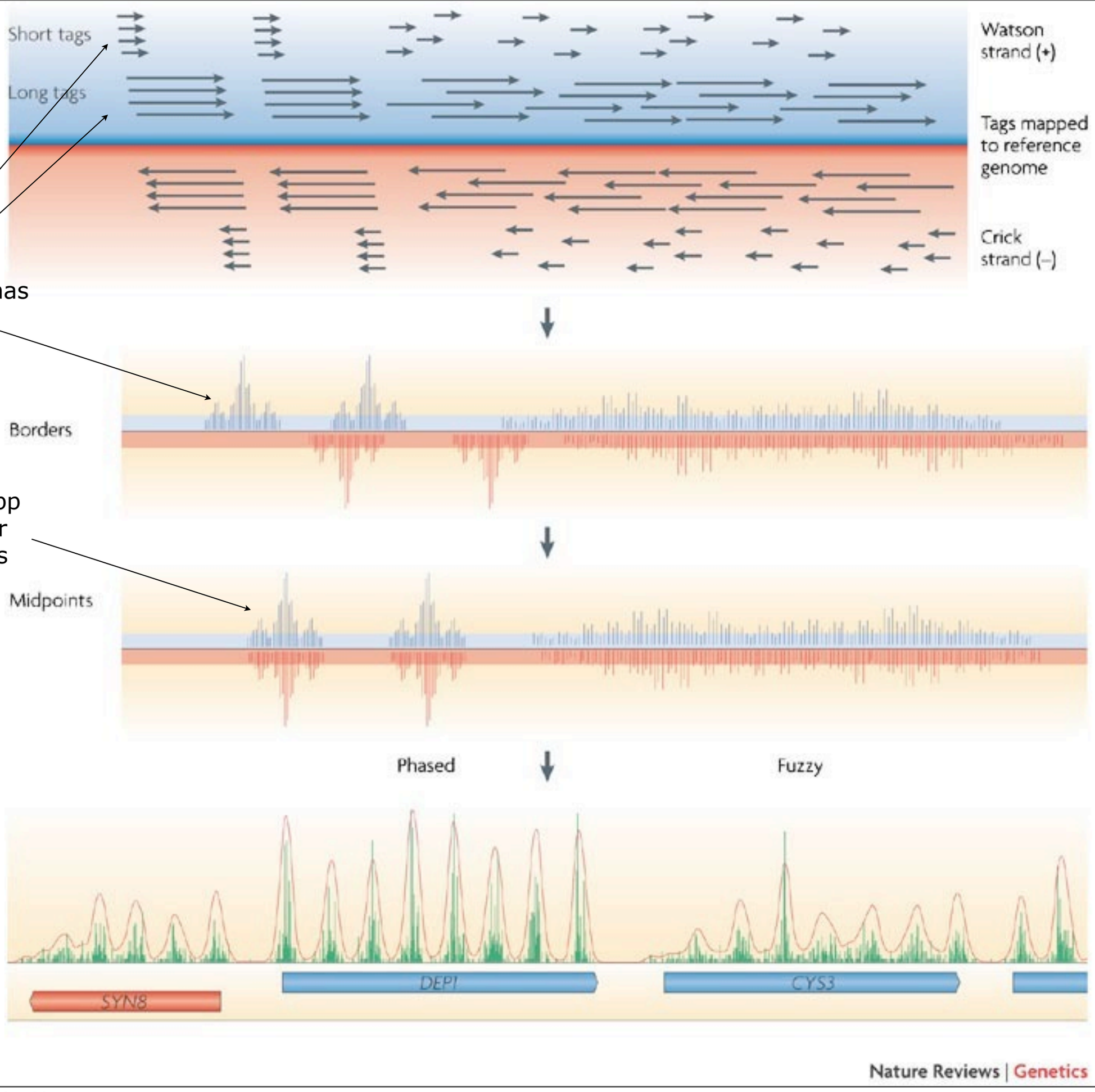


Acetliación per se no es suficiente para activación…

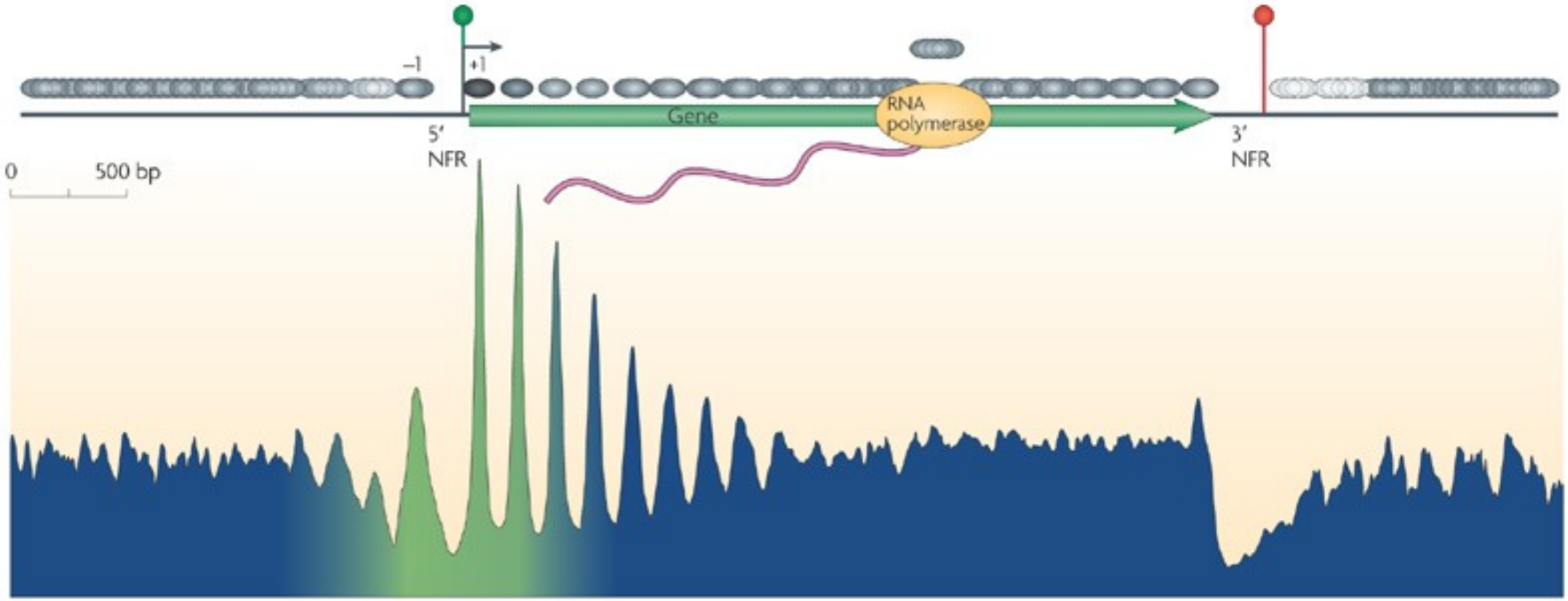


Bordes
de nucleosomas

+73bp o -73bp
para mapear
nucleosomas



Nature Reviews | Genetics



Nature Reviews | Genetics

Figure 2 | **Nucleosomal landscape of yeast genes.** The consensus distribution of nucleosomes (grey ovals) around all yeast genes is shown, aligned by the beginning and end of every gene. The resulting two plots were fused in the genic region. The peaks and valleys represent similar positioning relative to the transcription start site (TSS). The arrow under the green circle near the 5′ nucleosome-free region (NFR) represents the TSS. The green –blue shading in the plot represents the transitions observed in nucleosome composition and phasing (green represents high H2A.Z levels, acetylation, H3K4 methylation and phasing, whereas blue represents low levels of these modifications). The red circle indicates transcriptional termination within the 3′ NFR. Figure is reproduced, with permission, from