Regulation of Transcription in Eukaryotes

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Advances in PMB 2012

In eukaryotes gene expression is regulated at different levels

1 - Transcription
2 – Post-transcriptional modifications
3 – RNA transport
4 – Translation
5 - mRNA degradation
6 – Post- translational modifications

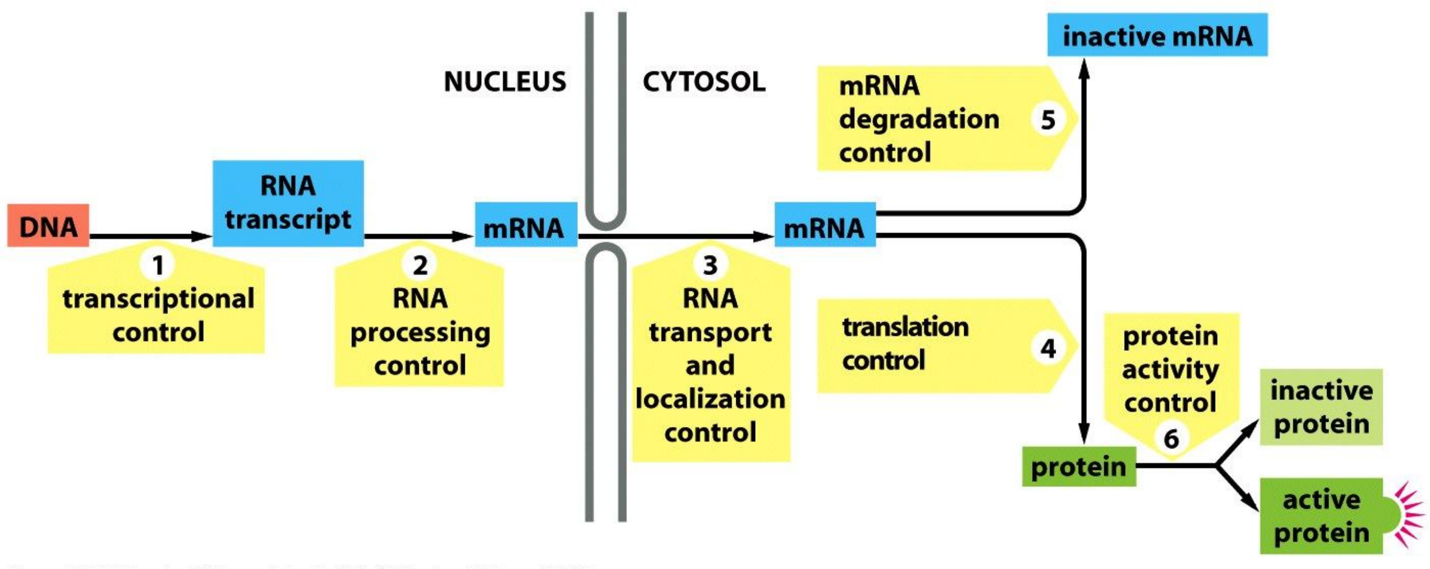
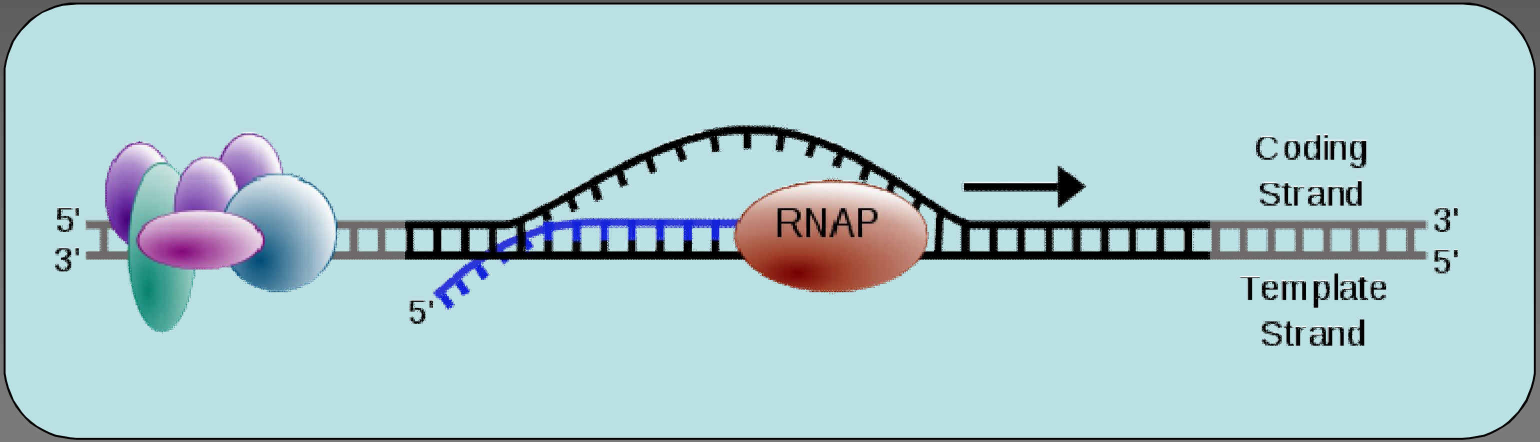


Figure 7-5 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Transcription

For most genes the initiation of RNA transcription is the most important point of control



Genetic analysis carried out in the 1950s provided the first evidence for the existence of gene regulatory proteins (“transcription factors”) that turn specific genes on or off.

Switching the tryptophan genes on and off

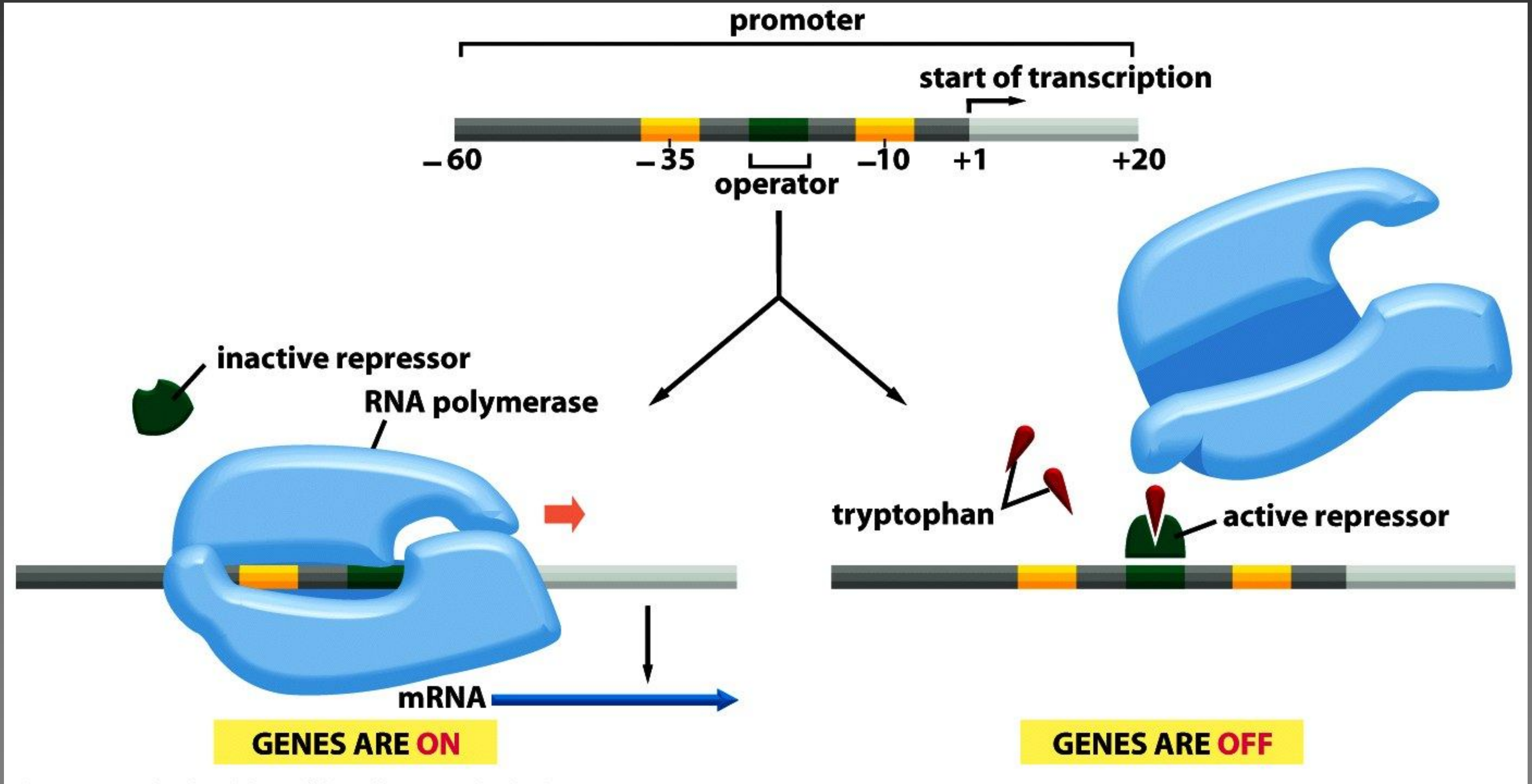


Figure 7-35 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Control of transcription in prokaryotes

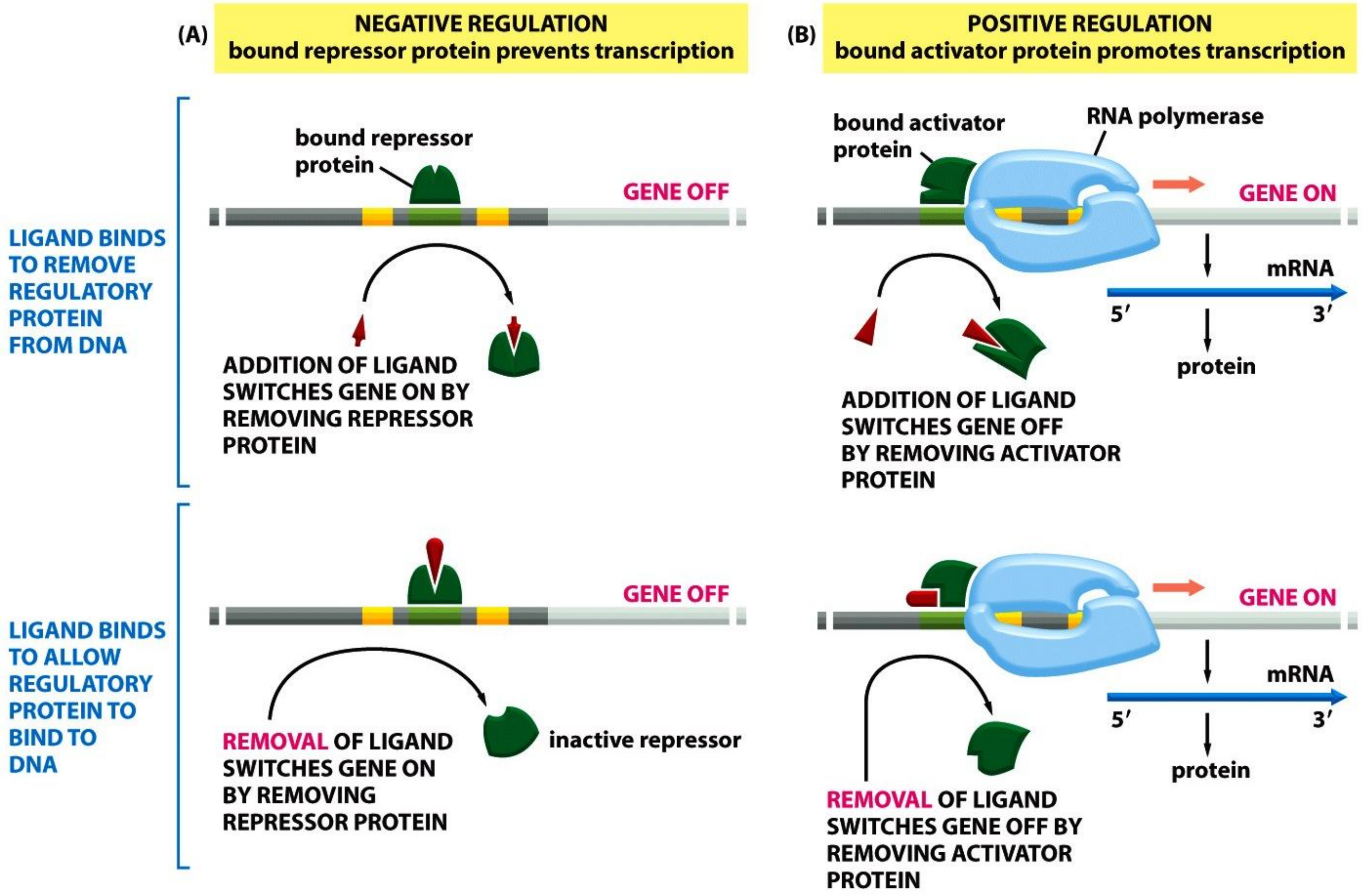


Figure 7-37 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Bacteria Sigma Factors to regulate gene transcription

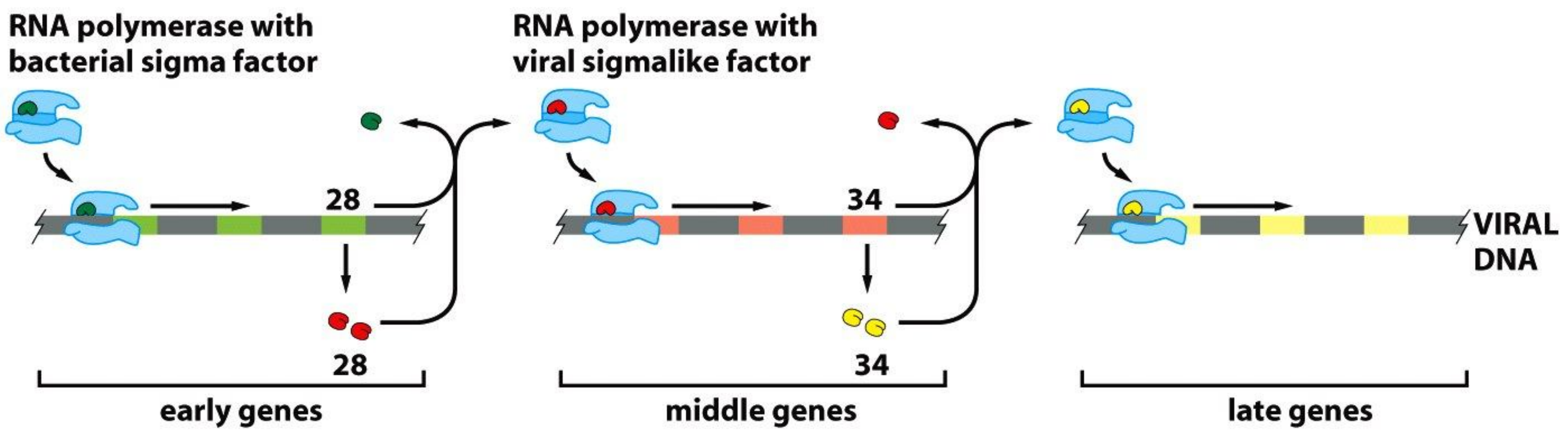
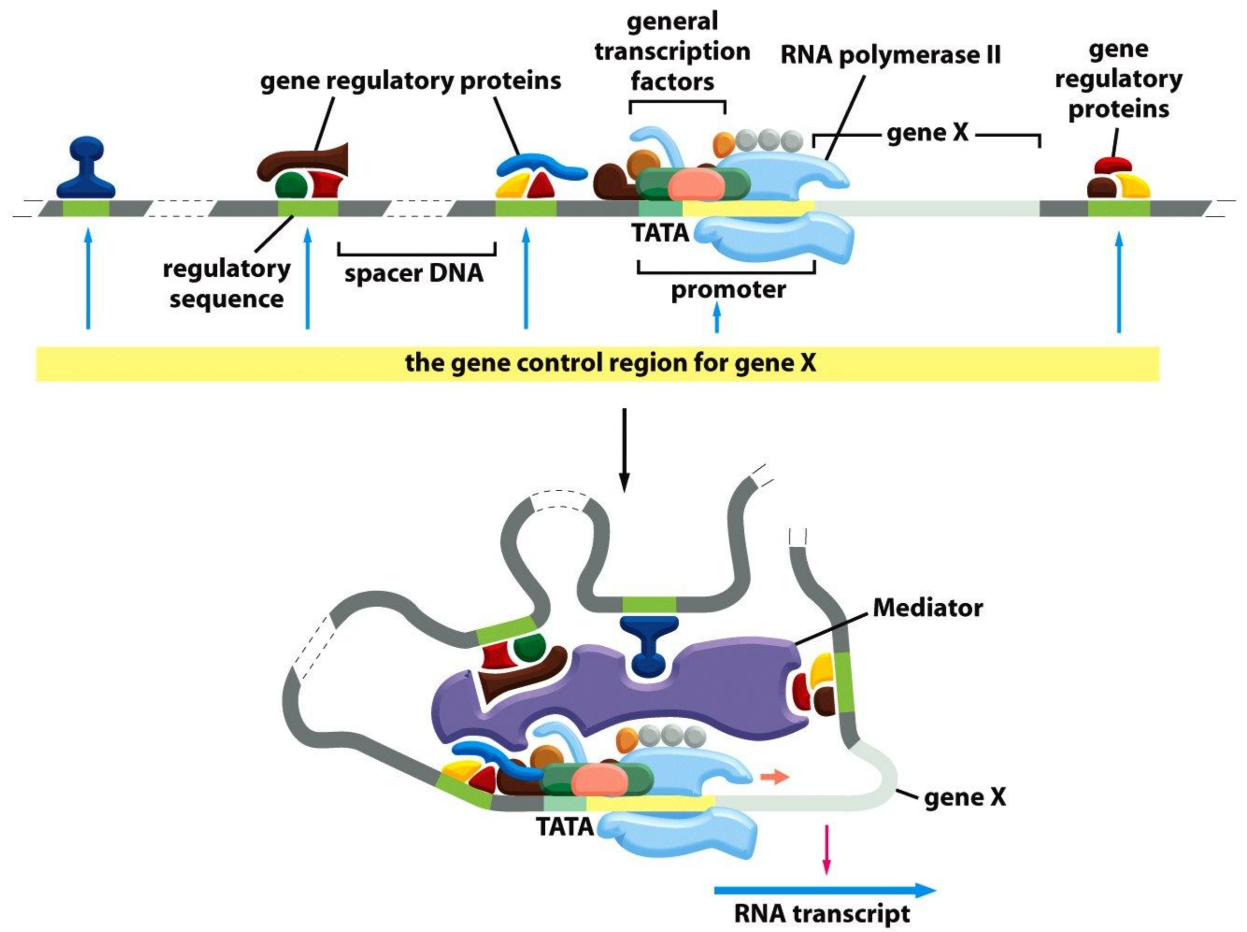


Figure 7-43 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Gene regulation in eukaryotes involves many more proteins



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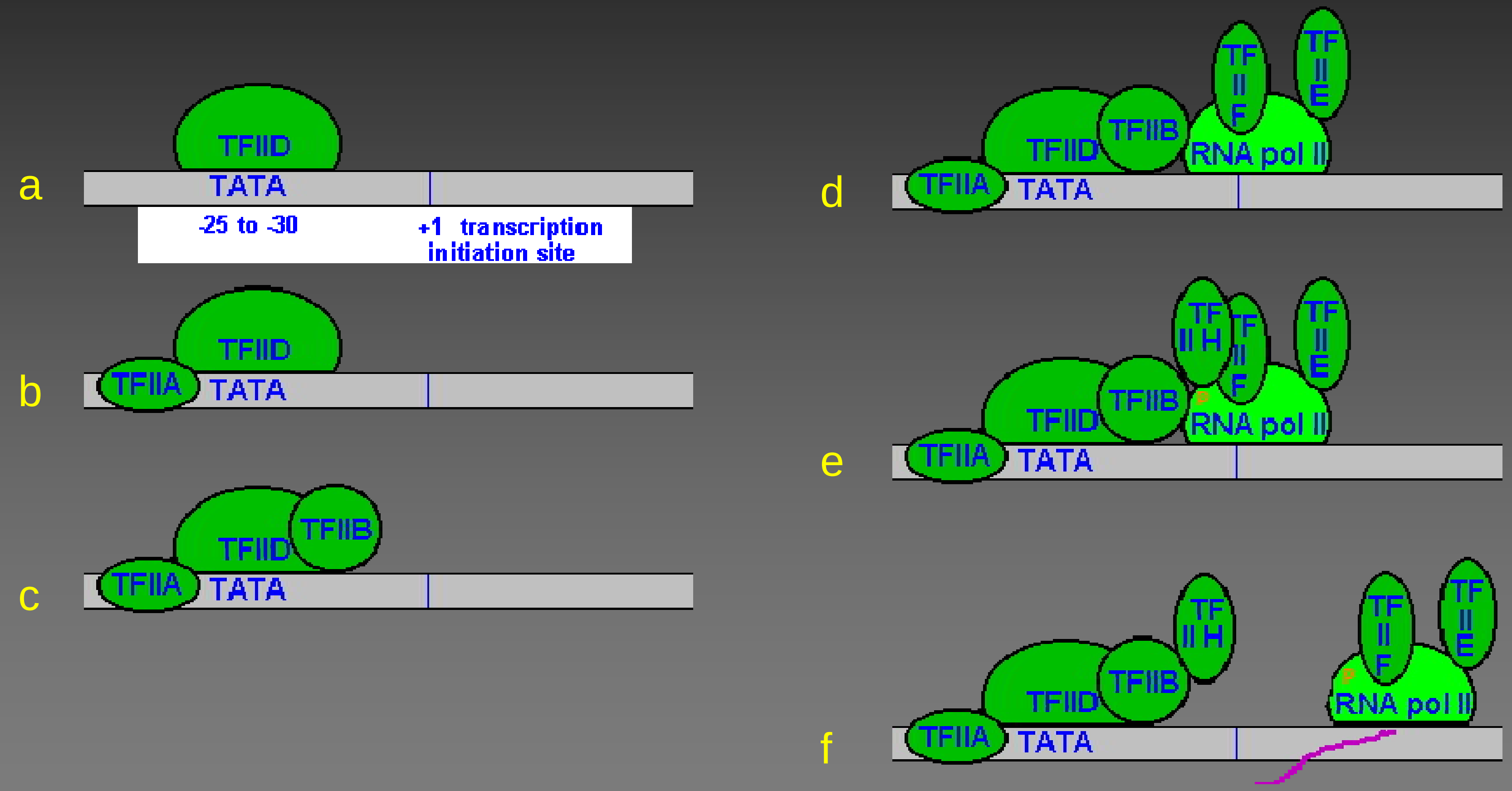
Transcription initiation in Eukaryotes



Transcription control

Prokaryotes	Eukaryotes
Bacterial RNA polymerase requires **1 general TFs,** the σ subunit	RNA polymerase II requires **5 general TFs**
Operons – sets of related genes transcribed as a unit	Regulate each **gene individually**
Each gene is controlled by **one or few regulatory proteins**	Controlled by **many** (sometimes hundreds) **regulatory proteins**, which may act over very large distances.
RNA polymerase is the only contact area for gene regulatory proteins	***Mediator***, a 24-subunit complex promotes the contact between RNA polymerase and regulatory proteins
Not available	**Chromatin** provides opportunities for transcriptional regulation

cis-elements are present in both prokaryotes and eukaryotes

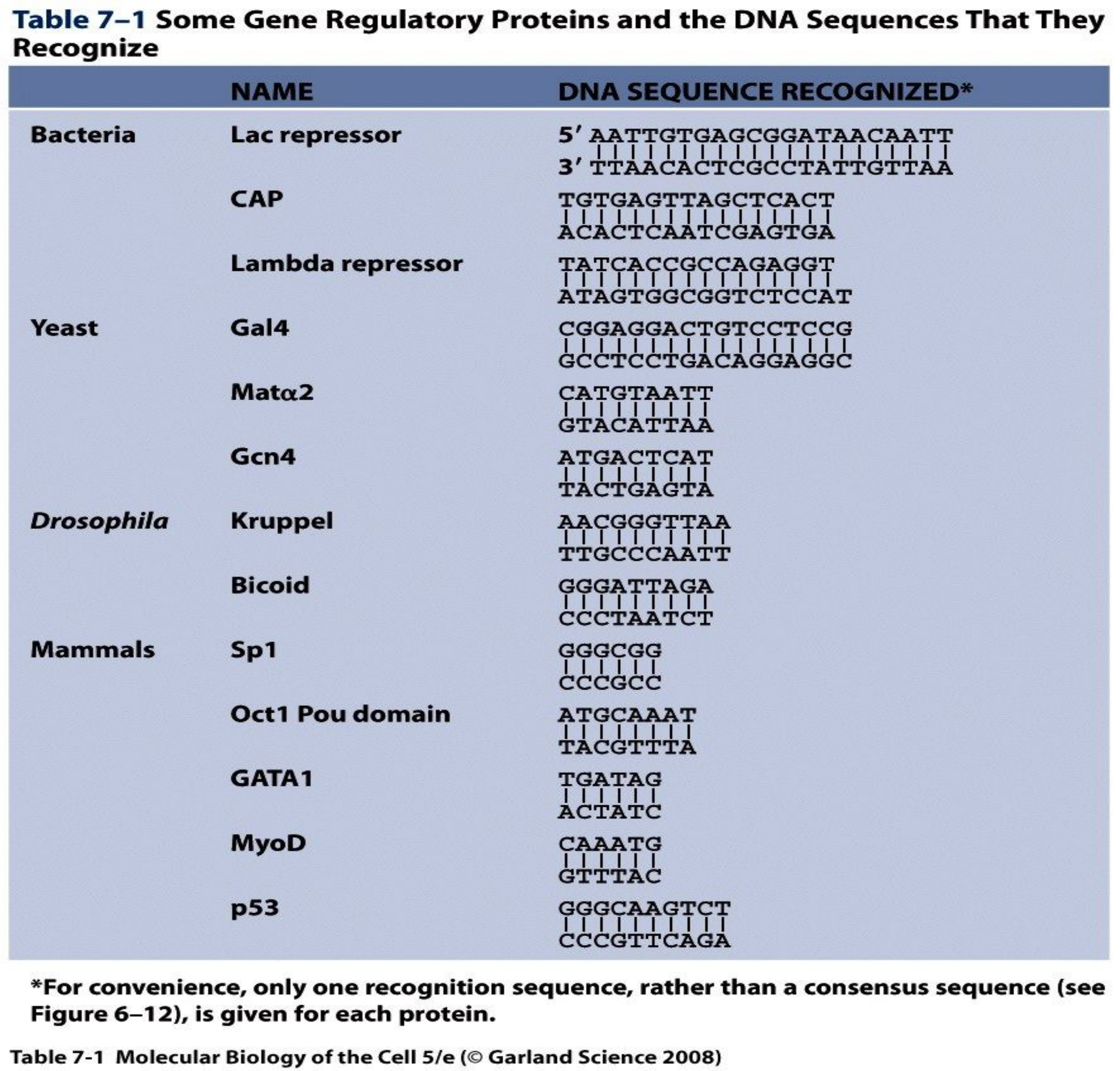


Table 7–1 Some Gene Regulatory Proteins and the DNA Sequences That They Recognize

	NAME	DNA SEQUENCE RECOGNIZED*
Bacteria	**Lac repressor**	5′ AATTGTGAGCGGATAACAATT 3′ TTAACACTCGCCTATTGTTAA
	CAP	TGTGAGTTAGCTCACT ACACTCAATCGAGTGA
	Lambda repressor	TATCACCGCCAGAGGT ATAGTGGCGGTCTCCAT
Yeast	**Gal4**	CGGAGGACTGTCCTCCG GCCTCCTGACAGGAGGC
	Matα2	CATGTAATT GTACATTAA
	Gcn4	ATGACTCAT TACTGAGTA
Drosophila	**Kruppel**	AACGGGTTAA TTGCCCAATT
	Bicoid	GGGATTAGA CCCTAATCT
Mammals	**Sp1**	GGGCGG CCCGCC
	Oct1 Pou domain	ATGCAAAT TACGTTTA
	GATA1	TGATAG ACTATC
	MyoD	CAAATG GTTTAC
	p53	GGGCAAGTCT CCCGTTCAGA

*For convenience, only one recognition sequence, rather than a consensus sequence (see Figure 6–12), is given for each protein.

Table 7-1 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Eukaryotes show three levels of transcriptional regulation

1 - Chromatin structure in gene regulation

2 - RNA and transcriptional modulation of gene expression

3 – Transcription factors regulating gene expression

Chromatin structure in gene regulation

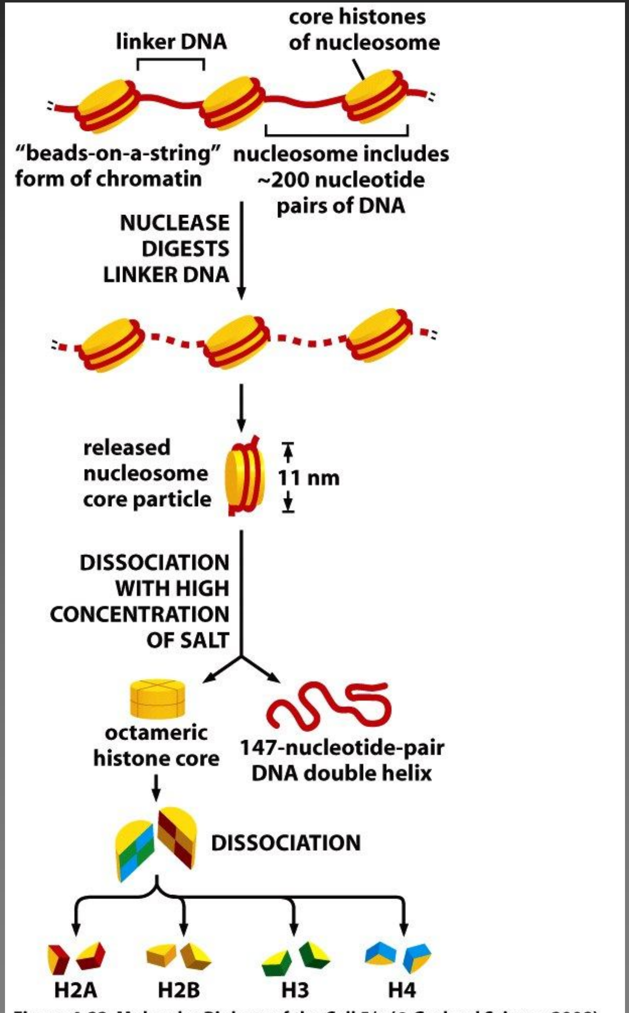


Figure 4-23 Molecular Biology of the Cell 5/e (© Garland Science 2008)

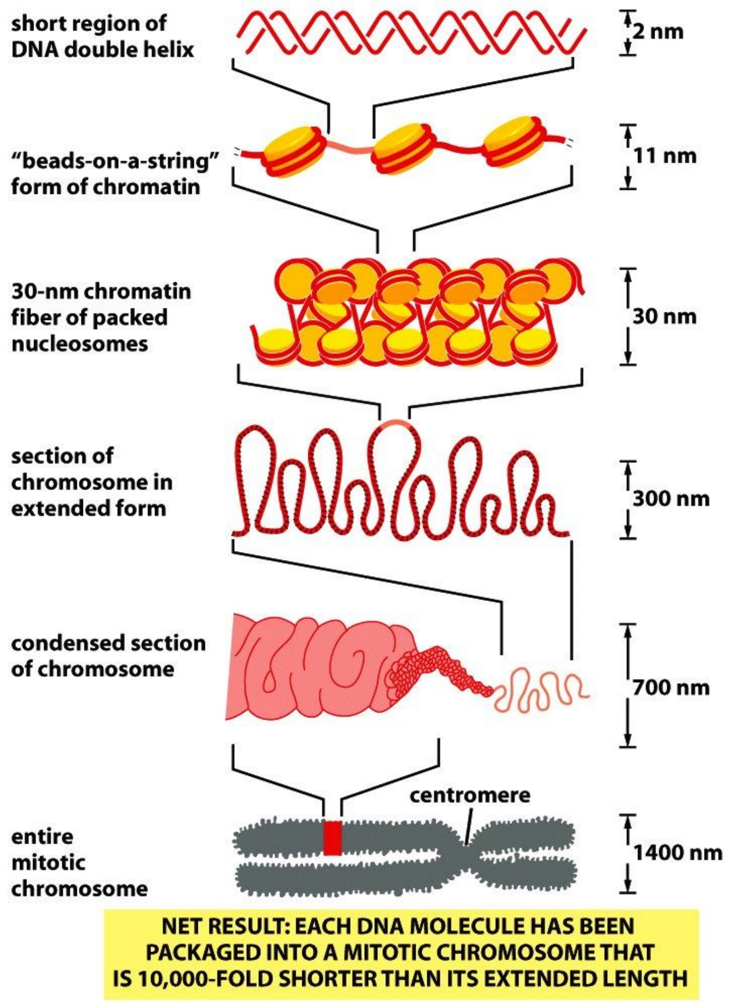


Figure 4-72 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Chromatin structure in gene regulation

Histone tails

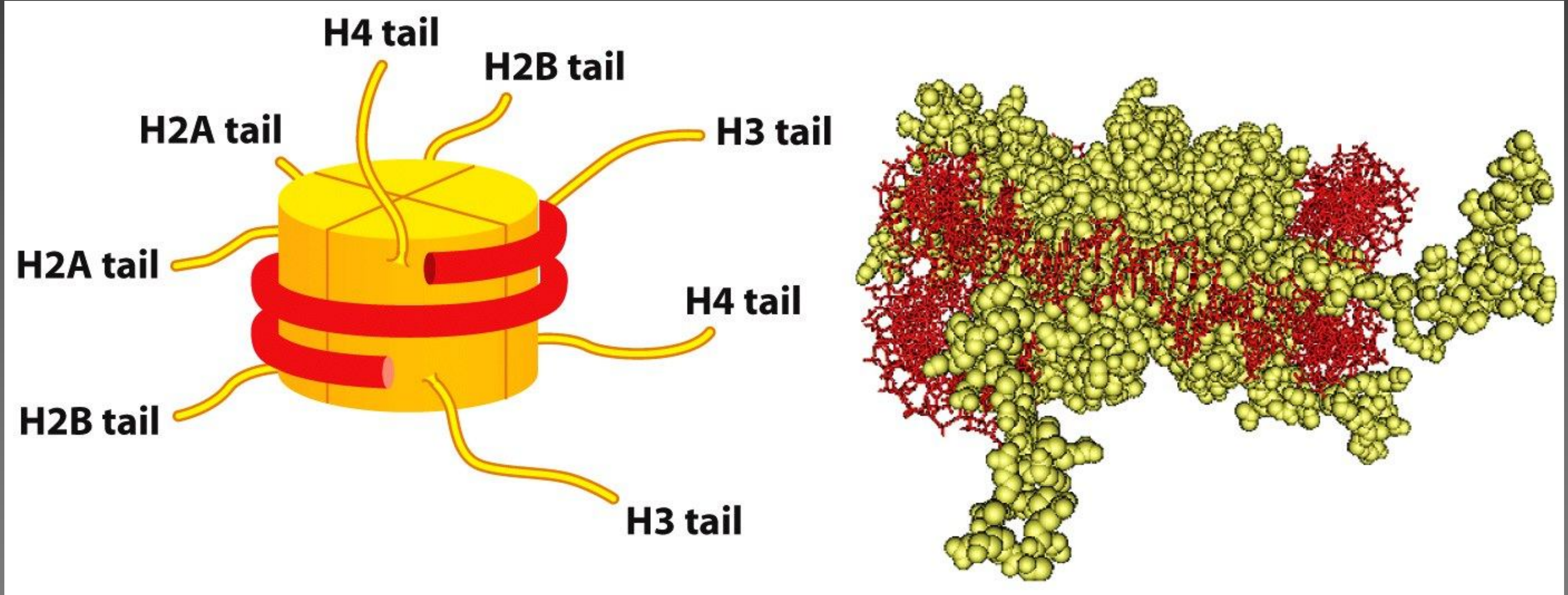


Figure 4-33a Molecular Biology of the Cell 5/e (© Garland Science 2008)

Chromatin structure in gene regulation

Histone code

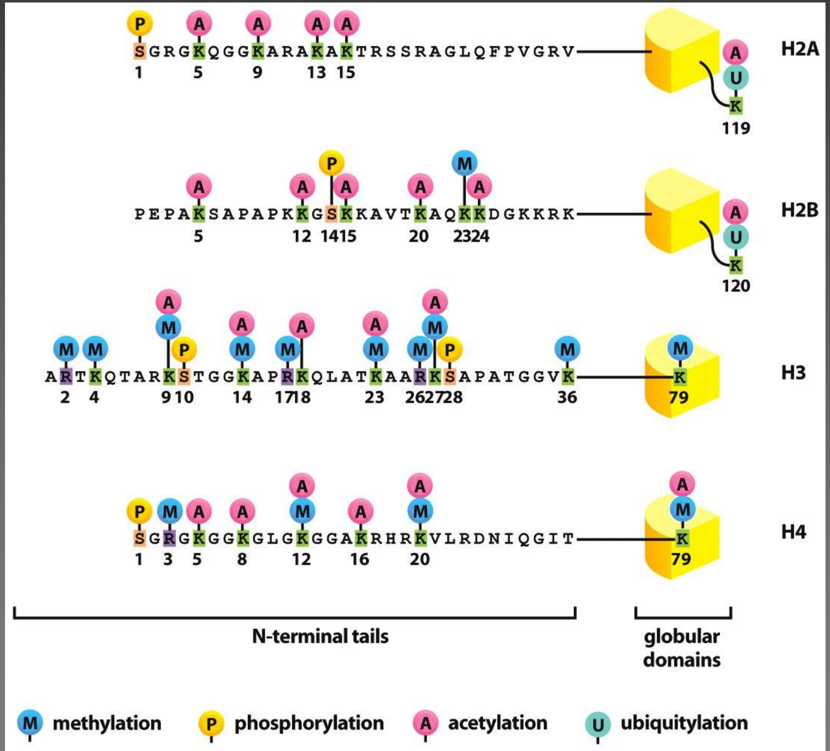


Figure 4-39b Molecular Biology of the Cell 5/e (© Garland Science 2008)

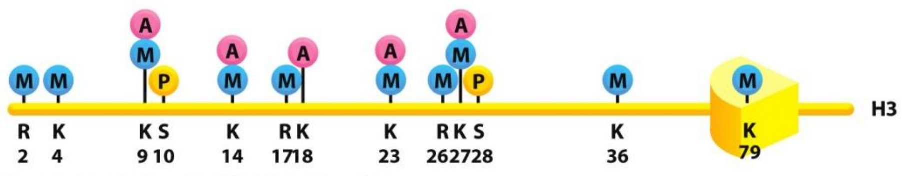


Figure 4-44a Molecular Biology of the Cell 5/e (© Garland Science 2008)

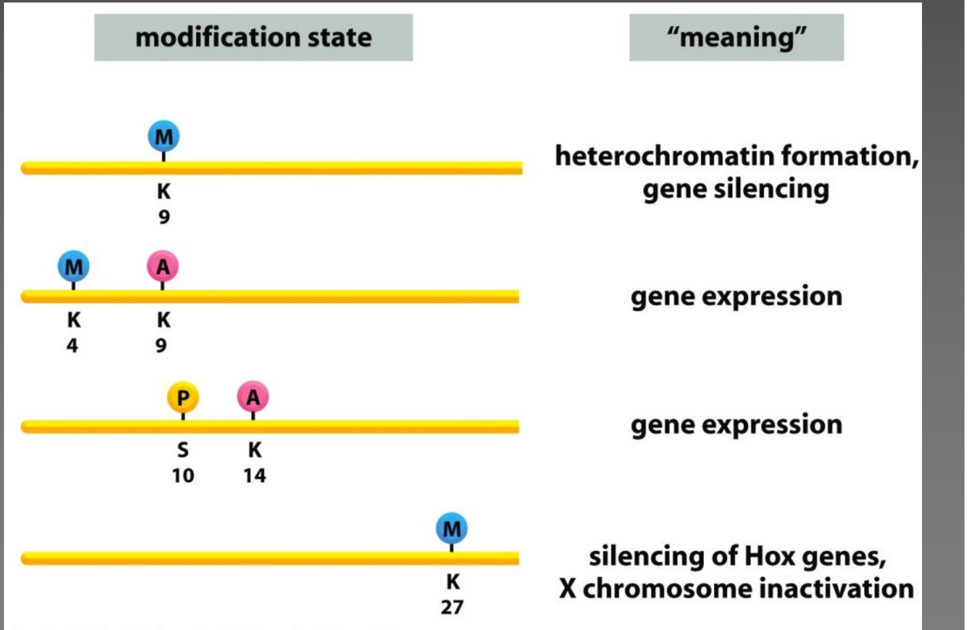
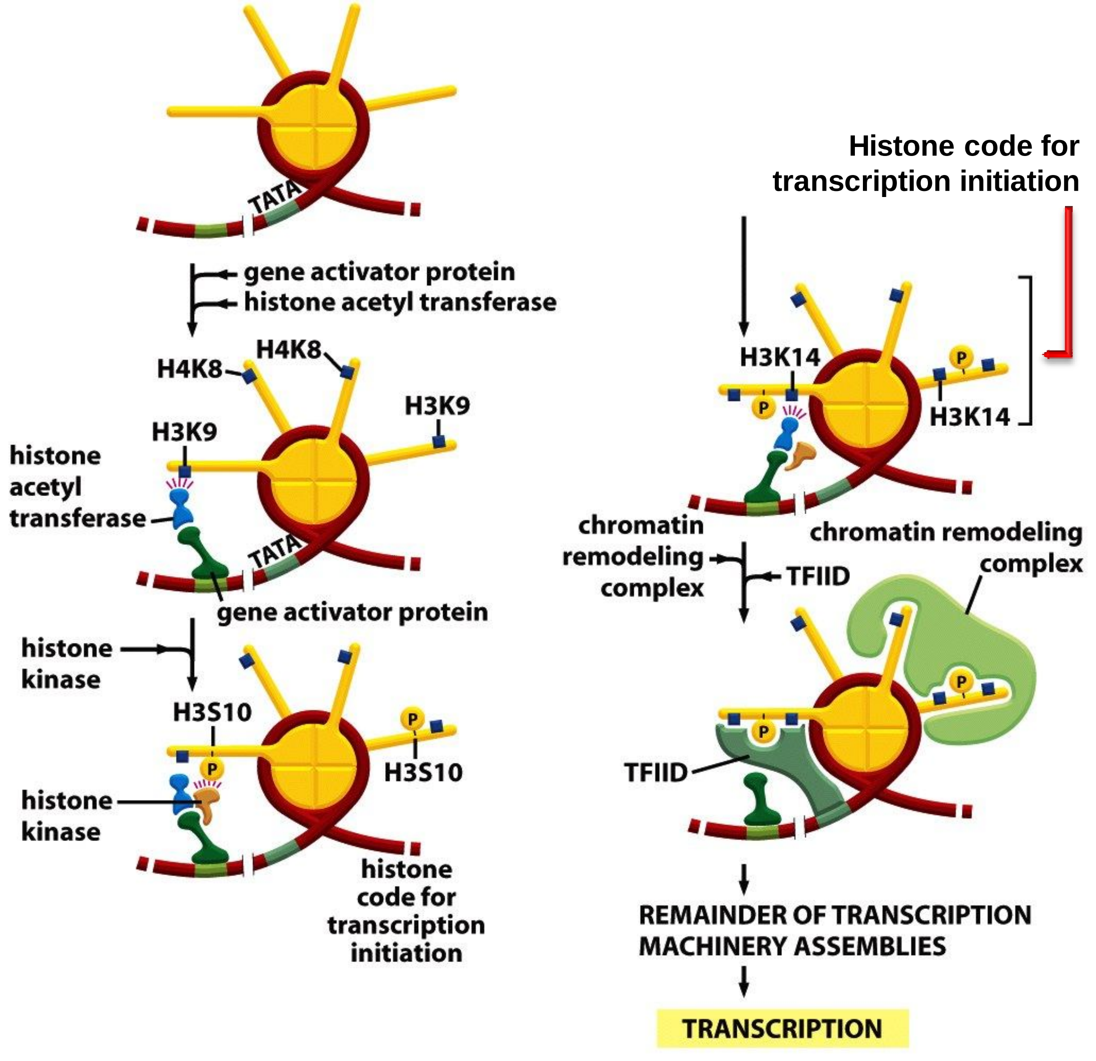


Figure 4-44b Molecular Biology of the Cell 5/e (© Garland Science 2008)

Chromatin structure in gene regulation

Writing and reading the histone code during transcription initiation



Chromatin structure in gene regulation

Activators alter chromatin structure to stimulate transcription initiation

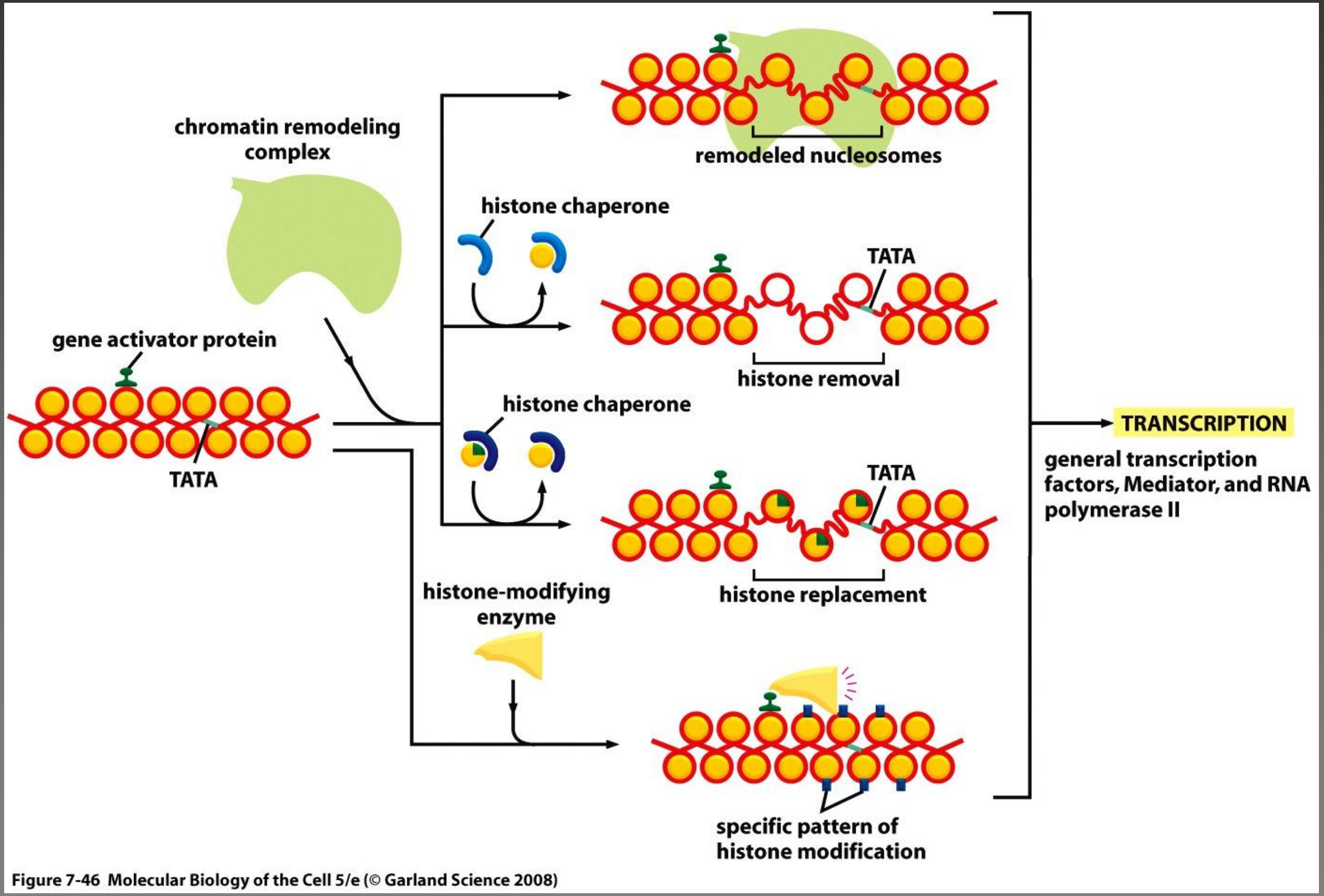


Figure 7-46 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Chromatin structure in gene regulation

Six ways in which eukaryotic gene repressors operate

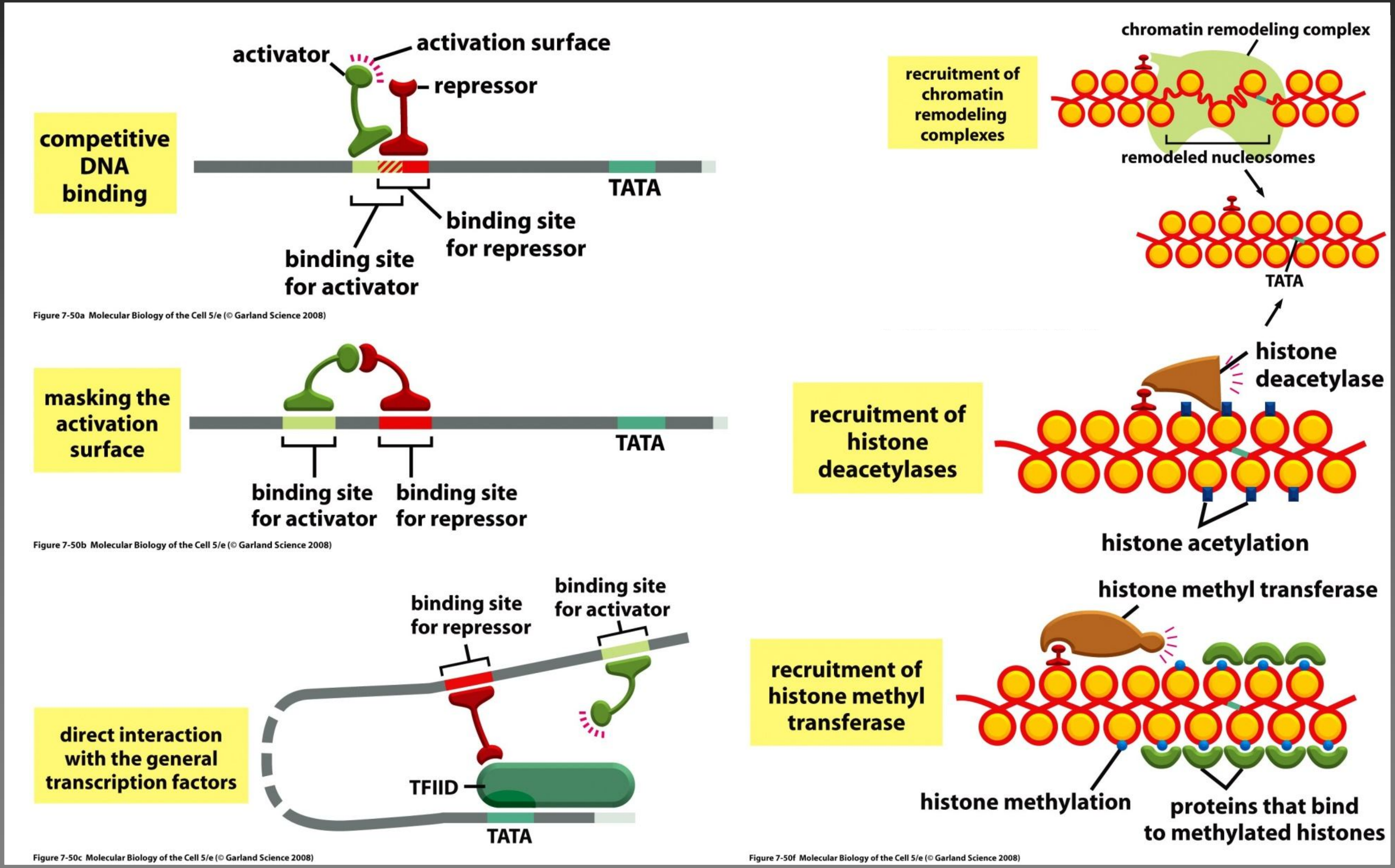


Figure 7-50a Molecular Biology of the Cell 5/e (© Garland Science 2008)

Figure 7-50b Molecular Biology of the Cell 5/e (© Garland Science 2008)

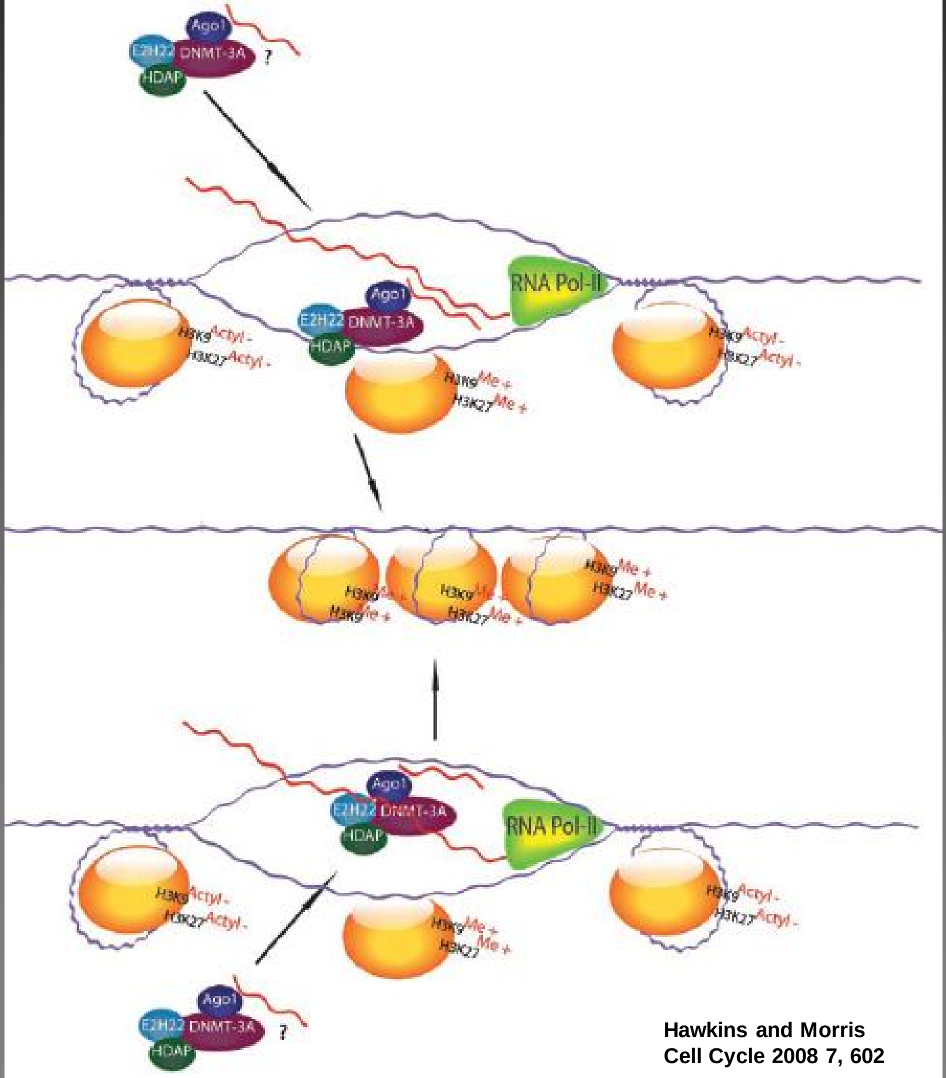
Figure 7-50c Molecular Biology of the Cell 5/e (© Garland Science 2008)

Figure 7-50f Molecular Biology of the Cell 5/e (© Garland Science 2008)

RNA and transcriptional modulation of gene expression

Small RNA directed TGS

Although the exact function of AGO1 and AGO2 in transcriptional silencing is not known, it is possible that the positively charged Argonaute proteins promote sequence-specific association between RNAs and their complementary targets



RNA/RNA

RNA/DNA

Hawkins and Morris
Cell Cycle 2008 7, 602

miRNA processing and mechanism of action

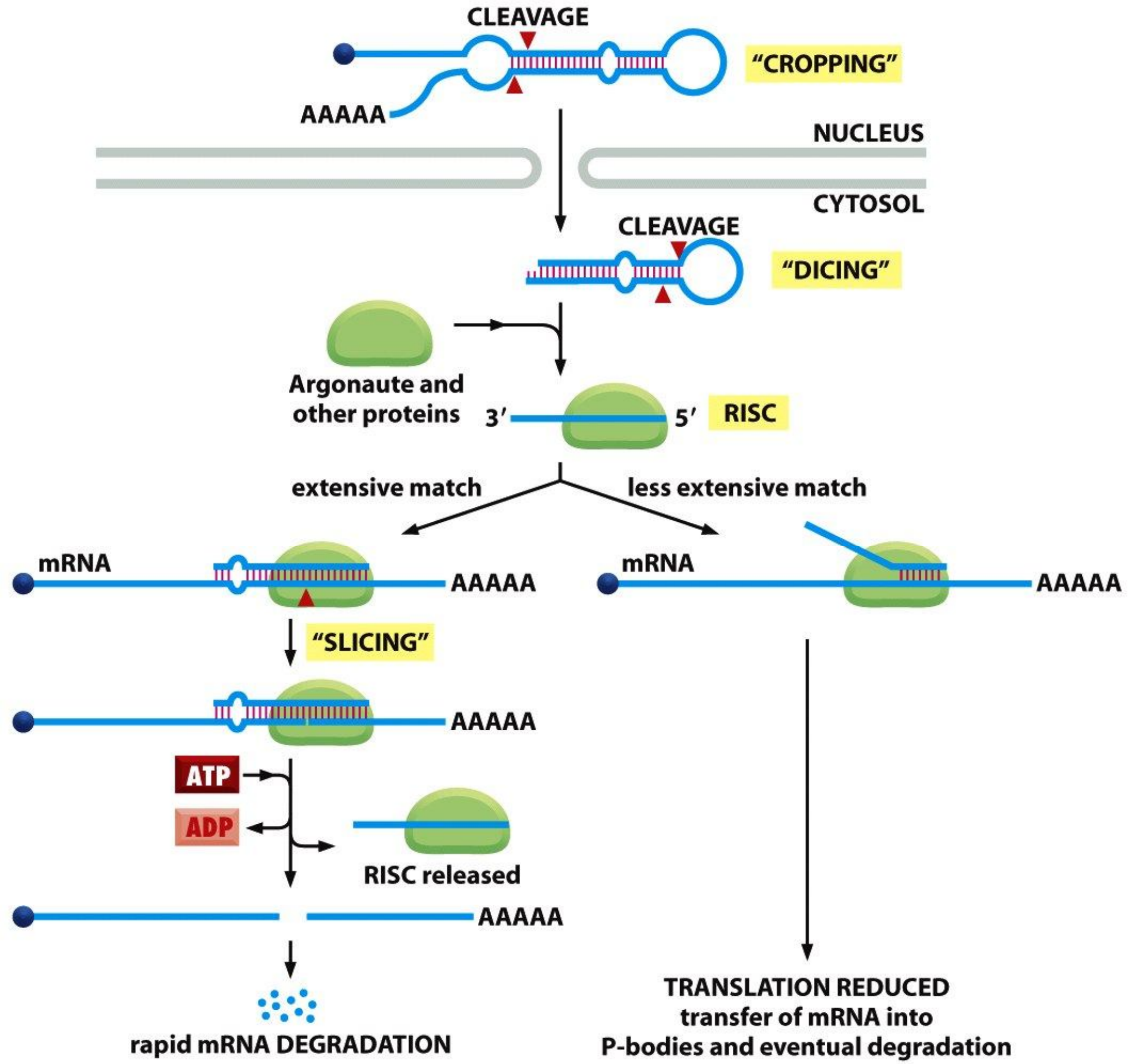


Figure 7-112 Molecular Biology of the Cell 5/e (© Garland Science 2008)

siRNA-mediated chromatin formation

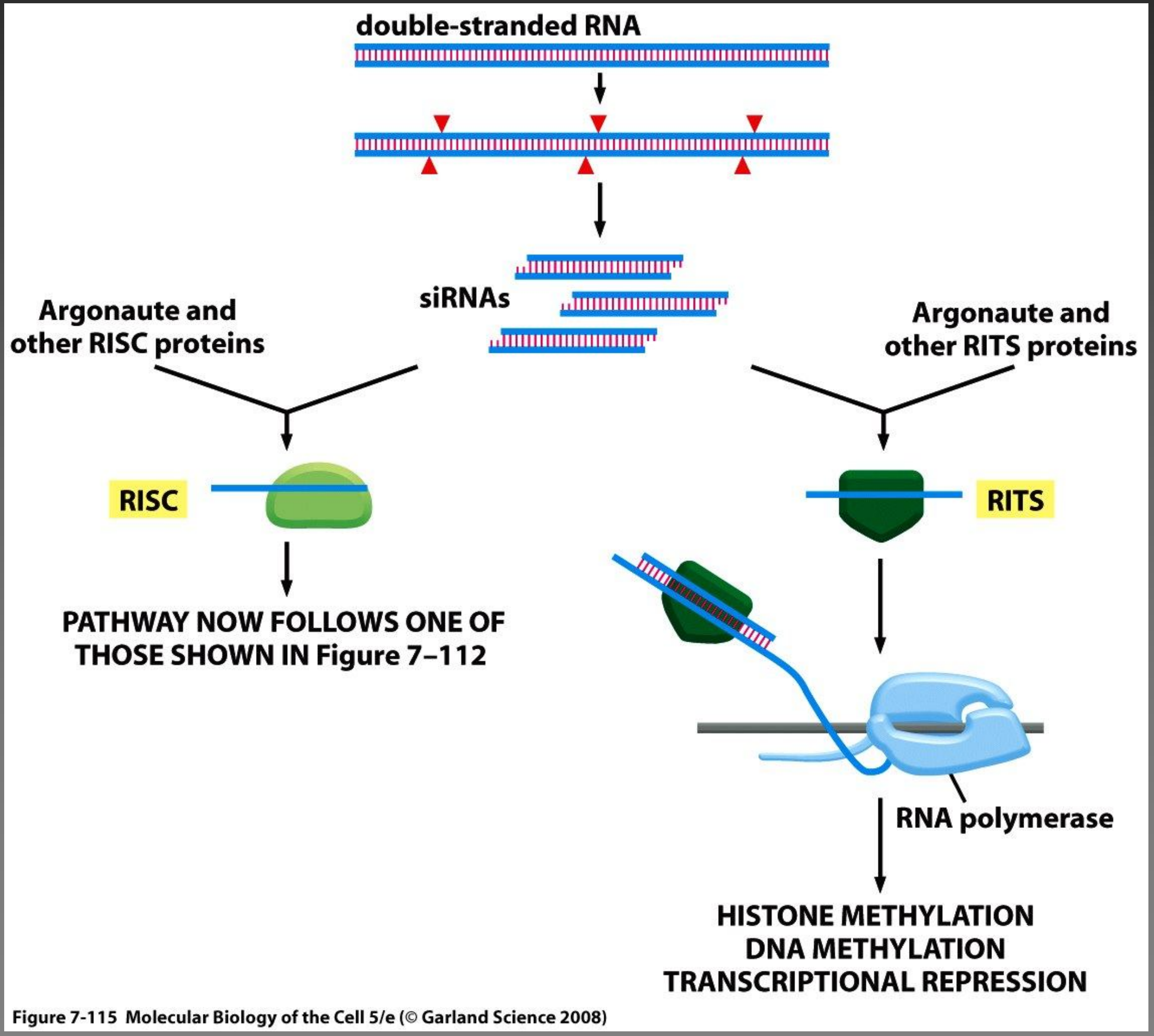
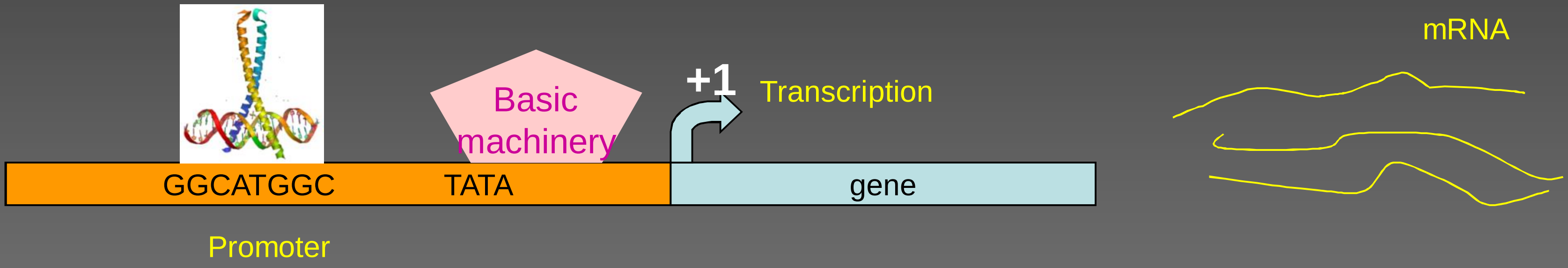


Figure 7-115 Molecular Biology of the Cell 5/e (© Garland Science 2008)

RITS (RNA-induced transcriptional silincing)

Transcription factors regulating gene expression

Transcription factors (TFs) - proteins that show sequence-specific DNA-binding and that are capable acivating or repressing gene transcription.



Transcription coregulators (coactivators/corepressors), chromatin remodelers, histone acetylases, kinases, and methylases play crucial roles in gene regulation, but lack DNA biding domains and therefore are not classified as TFs .

Schematic diagram of a prototypical transcription factor

TFs contain DNA-binding domain (**DBD**), signal sensing domain (**SSD**), and a transactivation domain (**TAD**)

The transactivation and signal sensing functions are frequently contained within the same domain

The order of placement and the number of domains may differ in various types of TFs

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Transcription factors regulating gene expression

Modular structure

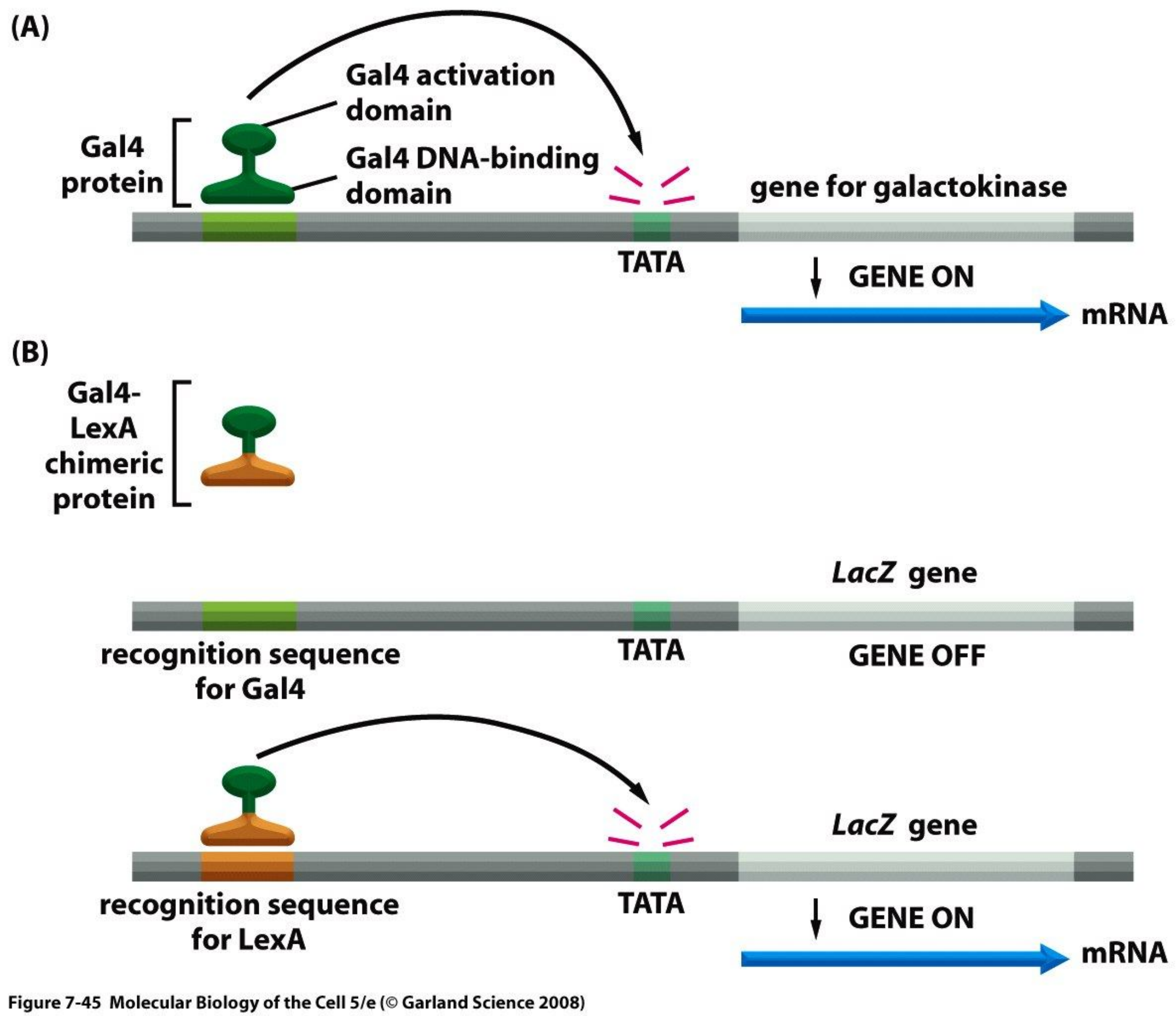


Figure 7-45 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Transcription factors regulating gene expression

Transcriptional synergy

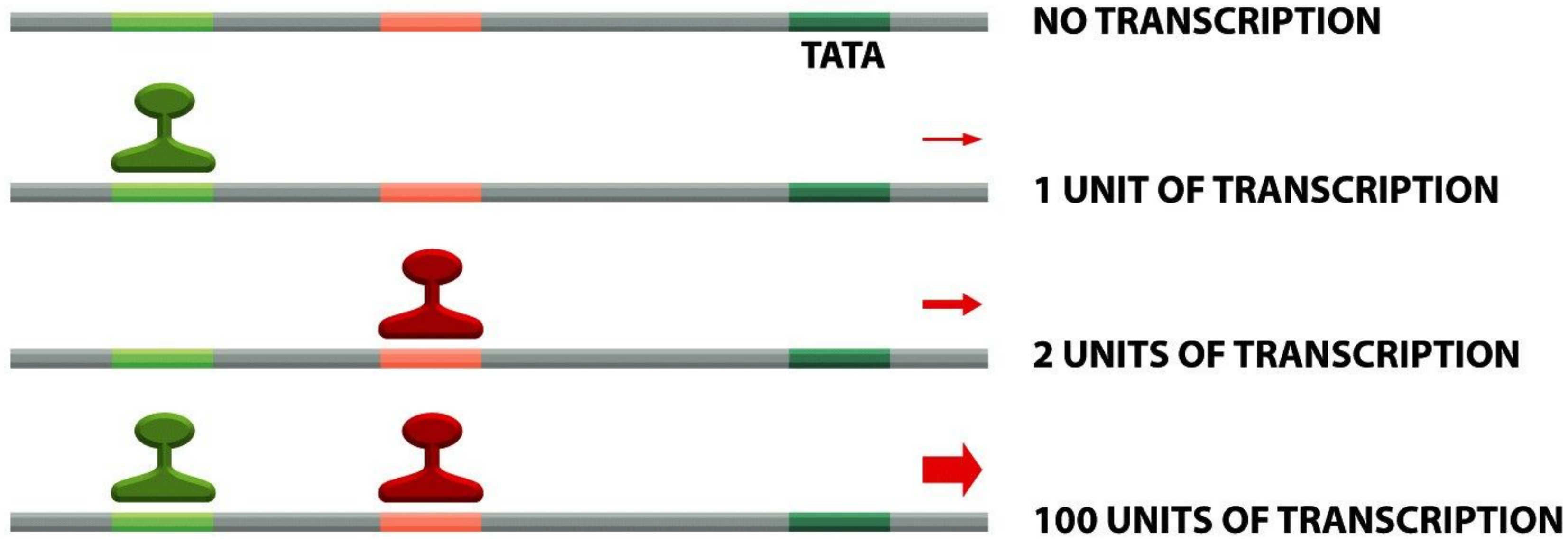


Figure 7-48 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Different types of tanscription factors

The DNA-binding helix-turn-helix motif

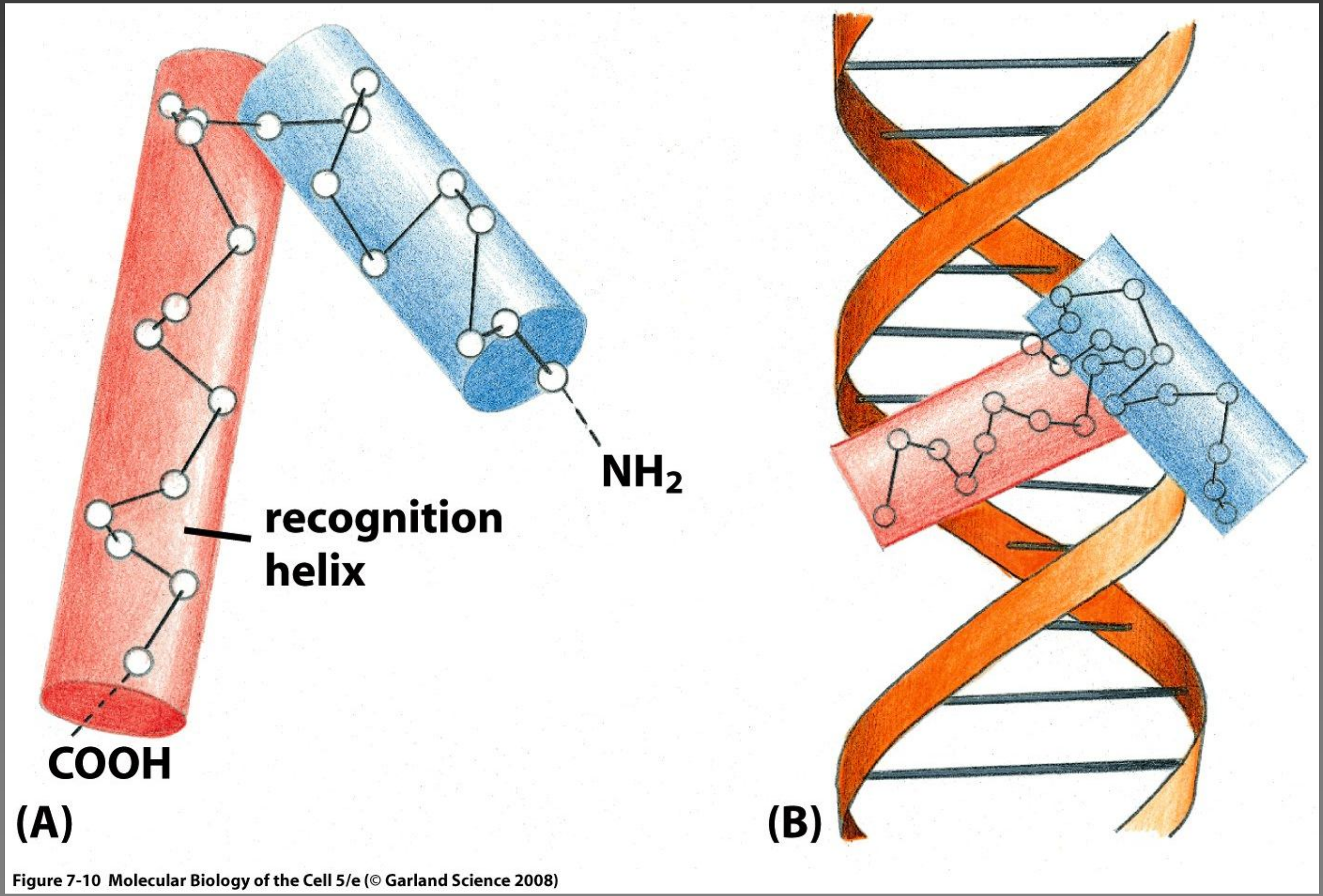


Figure 7-10 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Different types of TFs

DNA binding by a zinc finger protein

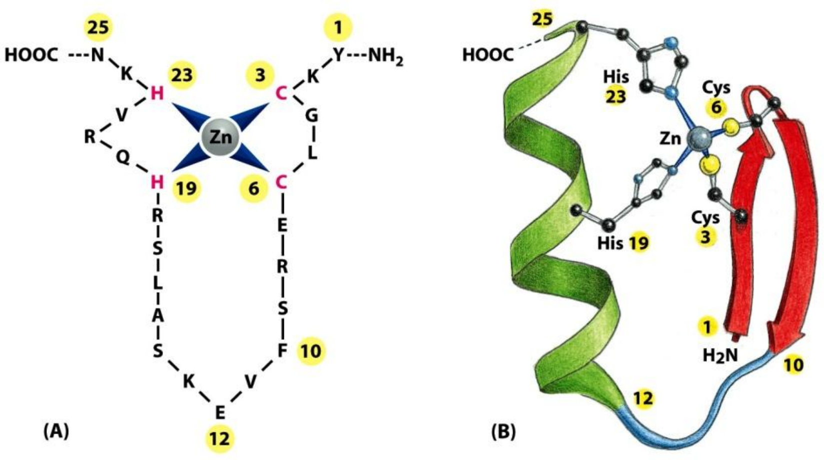


Figure 7-14 Molecular Biology of the Cell 5/e (© Garland Science 2008)

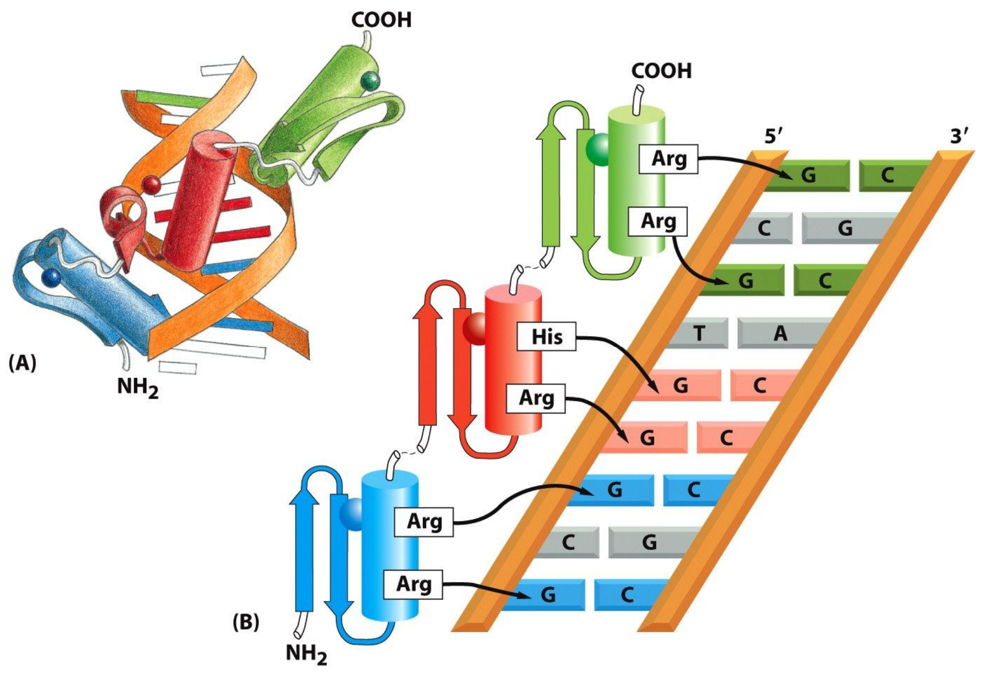
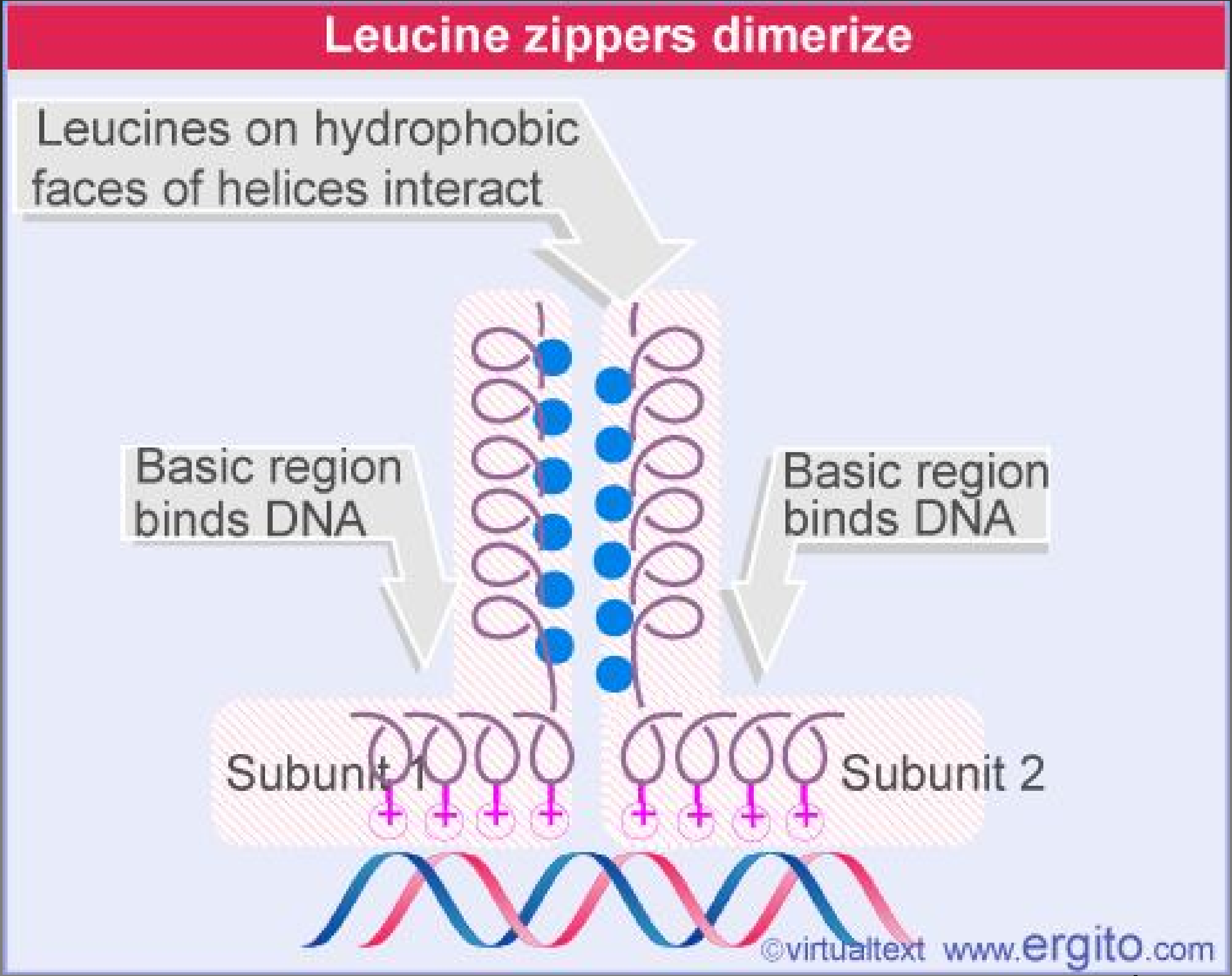


Figure 7-15 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Different types of TFs



Leucine zippers dimerize

Leucines on hydrophobic faces of helices interact

Basic region binds DNA

Basic region binds DNA

Different types of TFs

Heterodimerization of leucine zipper proteins

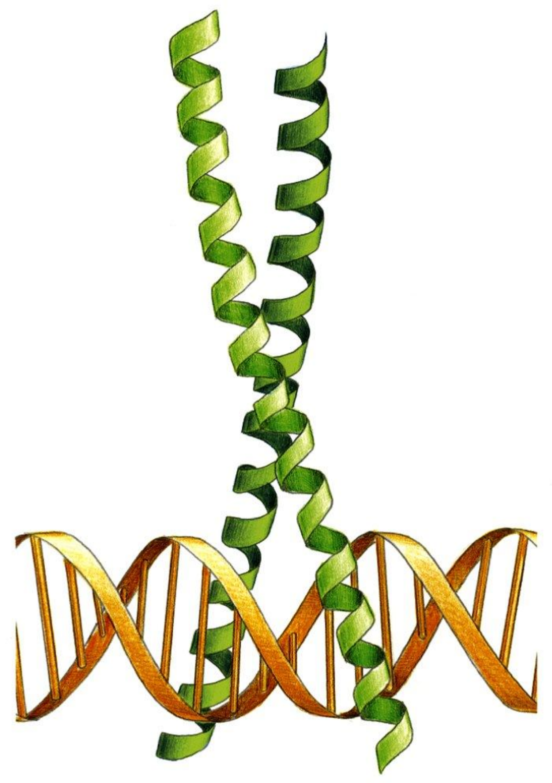


Figure 7-19 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Heterodimerization expands the repertoire of DNA sequences that TFs can recognize

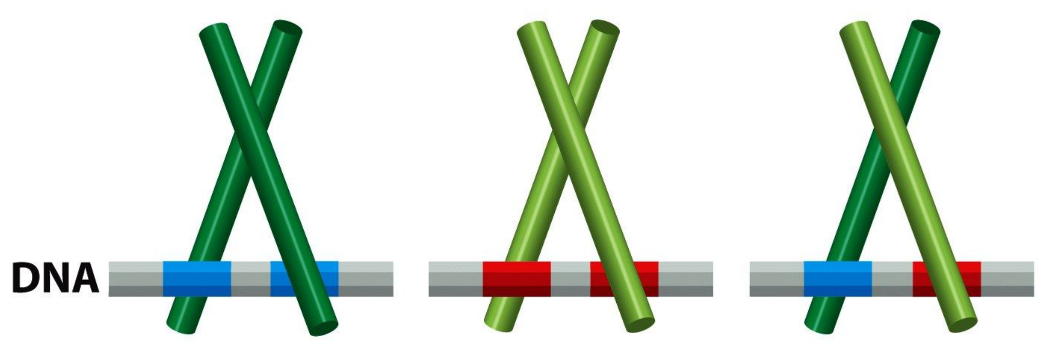


Figure 7-20 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Different types of TFs

Helix-Loop-Helix (HLH) dimer bound to DNA

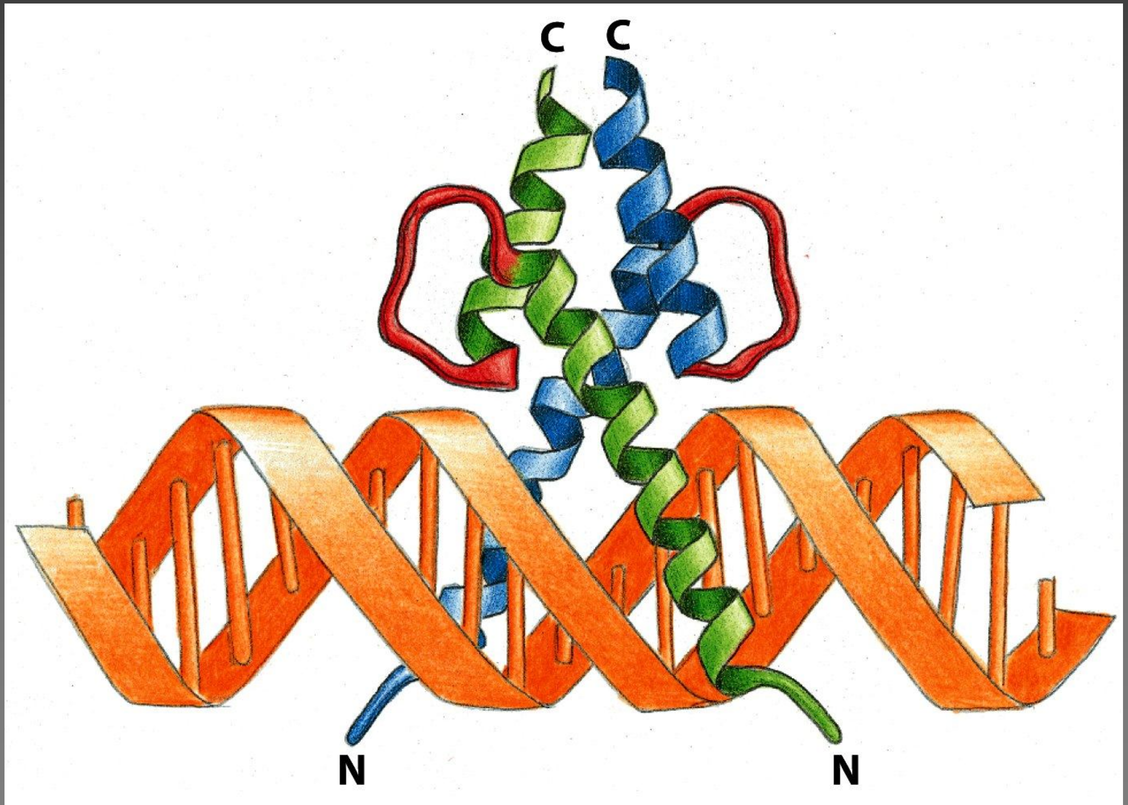


Figure 7-23 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Inhibitory regulation

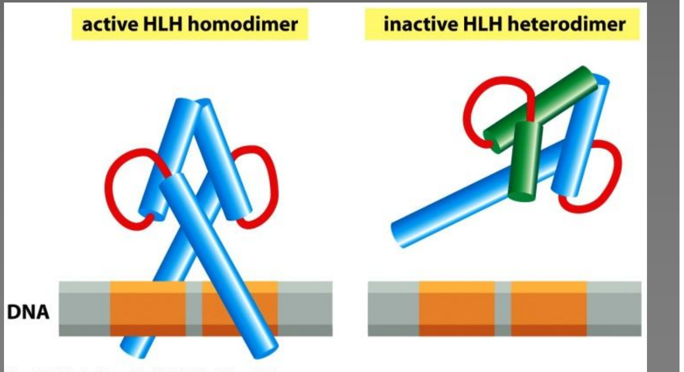
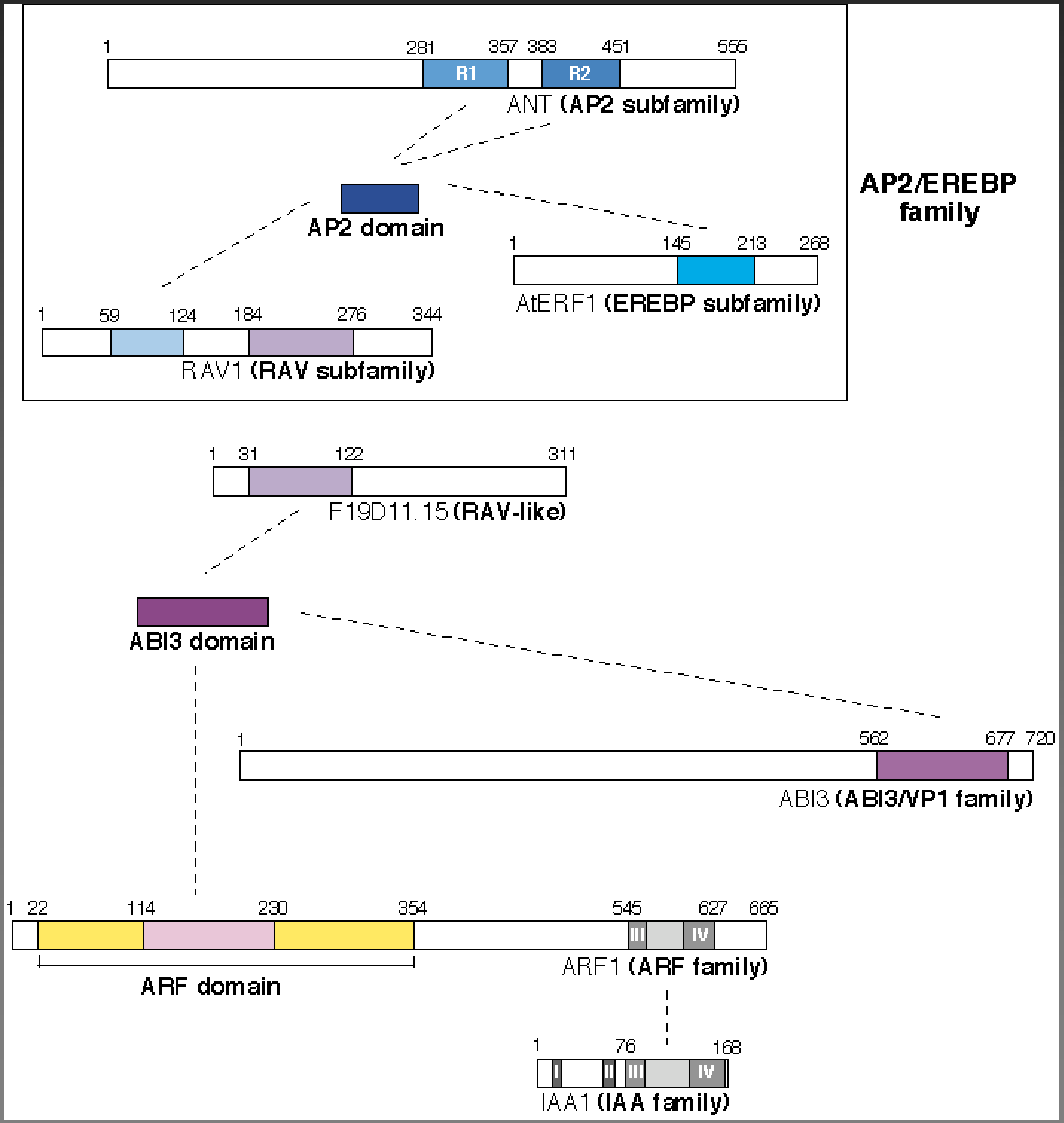


Figure 7-24 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Transcription Factor Families



DNA binding domain

↓

FAMILY

DNA binding domain(s)

+

(protein-protein interaction domains)

↓

Subfamily

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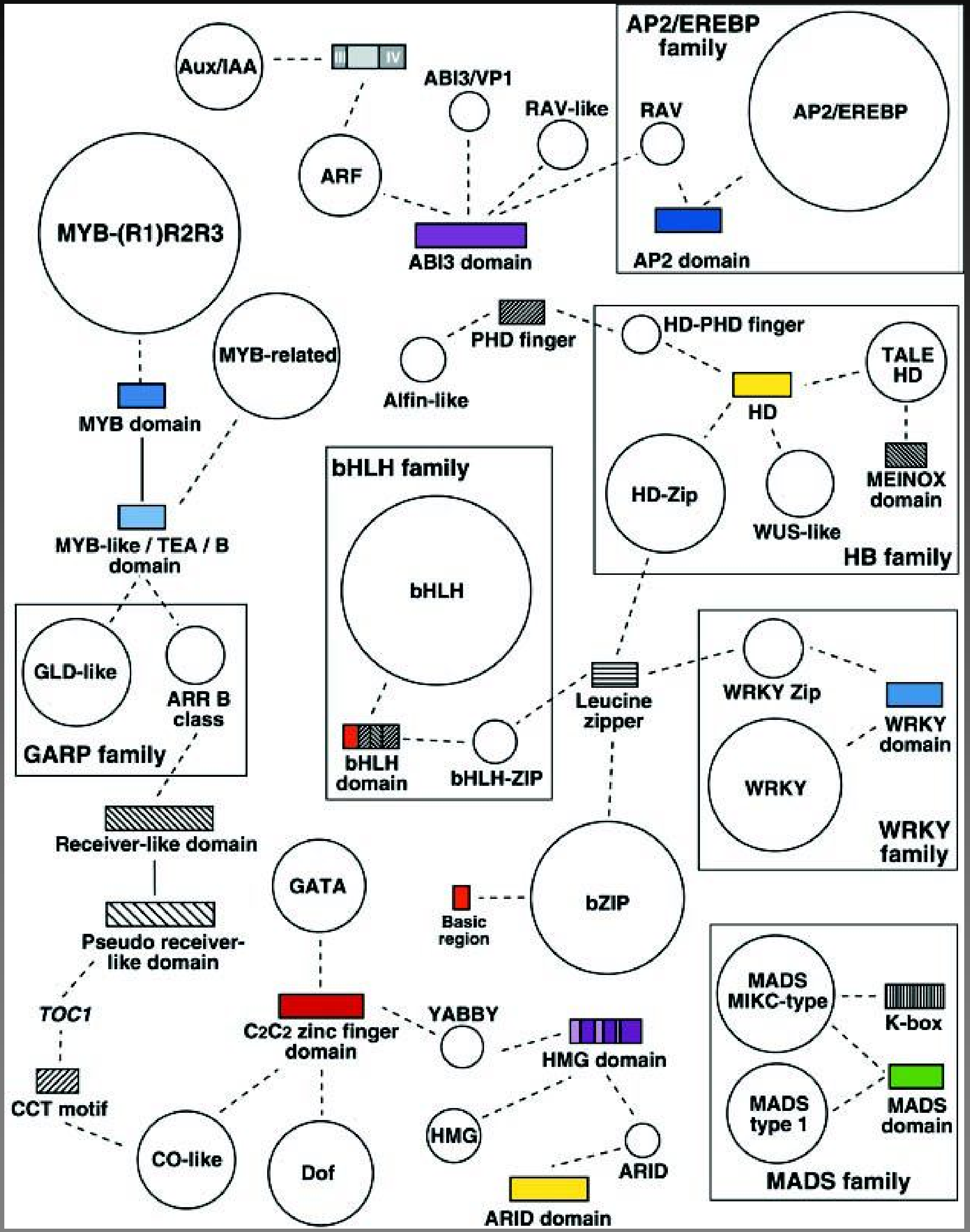
Arabidopsis Transcription Factors

~25.000 transcripts

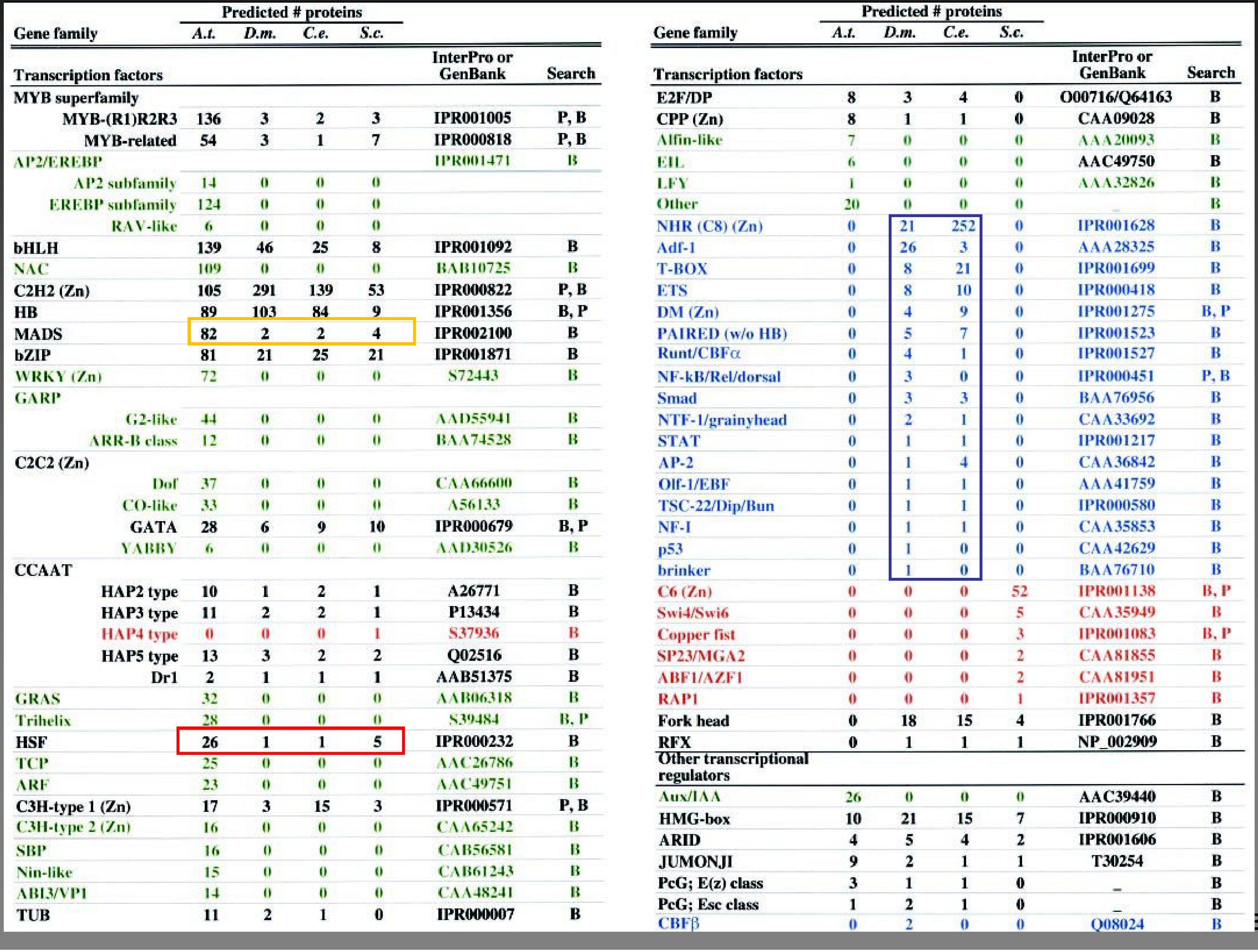
> 1500 TFs

Relationships and domain shuffling among the different Arabidopsis transcription factor families



Riechmann (2000) Science 290, 2105

Eukaryotic Transcriptional Regulators



Gene family	Predicted # proteins					
	A.t.	*D.m.*	*C.e.*	*S.c.*		
Transcription factors					InterPro or GenBank	Search
MYB superfamily						
MYB-(R1)R2R3	136	3	2	3	IPR001005	P, B
MYB-related	54	3	1	7	IPR000818	P, B
AP2/EREBP					IPR001471	B
AP2 subfamily	14	0	0	0		
EREBP subfamily	124	0	0	0		
RAV-like	6	0	0	0		
bHLH	139	46	25	8	IPR001092	B
NAC	109	0	0	0	BAB10725	B
C2H2 (Zn)	105	291	139	53	IPR000822	P, B
HB	89	103	84	9	IPR001356	B, P
MADS	82	2	2	4	IPR002100	B
bZIP	81	21	25	21	IPR001871	B
WRKY (Zn)	72	0	0	0	S72443	B
GARP						
G2-like	44	0	0	0	AAD55941	B
ARR-B class	12	0	0	0	BAA74528	B
C2C2 (Zn)						
Dof	37	0	0	0	CAA66600	B
CO-like	33	0	0	0	A56133	B
GATA	28	6	9	10	IPR000679	B, P
YABBY	6	0	0	0	AAD30526	B
CCAAT						
HAP2 type	10	1	2	1	A26771	B
HAP3 type	11	2	2	1	P13434	B
HAP4 type	0	0	0	1	S37936	B
HAP5 type	13	3	2	2	Q02516	B
Dr1	2	1	1	1	AAB51375	B
GRAS	32	0	0	0	AAB06318	B
Trihelix	28	0	0	0	S39484	B, P
HSF	26	1	1	5	IPR000232	B
TCP	25	0	0	0	AAC26786	B
ARF	23	0	0	0	AAC49751	B
C3H-type 1 (Zn)	17	3	15	3	IPR000571	P, B
C3H-type 2 (Zn)	16	0	0	0	CAA65242	B
SBP	16	0	0	0	CAB56581	B
Nin-like	15	0	0	0	CAB61243	B
ABI3/VP1	14	0	0	0	CAA48241	B
TUB	11	2	1	0	IPR000007	B
E2F/DP	8	3	4	0	O00716/Q64163	B
CPP (Zn)	8	1	1	0	CAA09028	B
Alfin-like	7	0	0	0	AAA20093	B
EIL	6	0	0	0	AAC49750	B
LFY	1	0	0	0	AAA32826	B
Other	20	0	0	0	–	B
NHR (C8) (Zn)	0	21	252	0	IPR001628	B
Adf-1	0	26	3	0	AAA28325	B
T-BOX	0	8	21	0	IPR001699	B
ETS	0	8	10	0	IPR000418	B
DM (Zn)	0	4	9	0	IPR001275	B, P
PAIRED (w/o HB)	0	5	7	0	IPR001523	B
Runt/CBFα	0	4	1	0	IPR001527	B
NF-kB/Rel/dorsal	0	3	0	0	IPR000451	P, B
Smad	0	3	3	0	BAA76956	B
NTF-1/grainyhead	0	2	1	0	CAA33692	B
STAT	0	1	1	0	IPR001217	B
AP-2	0	1	4	0	CAA36842	B
Olf-1/EBF	0	1	1	0	AAA41759	B
TSC-22/Dip/Bun	0	1	1	0	IPR000580	B
NF-I	0	1	1	0	CAA35853	B
p53	0	1	0	0	CAA42629	B
brinker	0	1	0	0	BAA76710	B
C6 (Zn)	0	0	0	52	IPR001138	B, P
Swi4/Swi6	0	0	0	5	CAA35949	B
Copper fist	0	0	0	3	IPR001083	B, P
SP23/MGA2	0	0	0	2	CAA81855	B
ABF1/AZF1	0	0	0	2	CAA81951	B
RAP1	0	0	0	1	IPR001357	B
Fork head	0	18	15	4	IPR001766	B
RFX	0	1	1	1	NP_002909	B
Other transcriptional regulators						
Aux/IAA	26	0	0	0	AAC39440	B
HMG-box	10	21	15	7	IPR000910	B
ARID	4	5	4	2	IPR001606	B
JUMONJI	9	2	1	1	T30254	B
PcG; E(z) class	3	1	1	0	–	B
PcG; Esc class	1	2	1	0	–	B
CBFβ	0	2	0	0	Q08024	B

Plant TF families and their function

AP2/ERF	**(144)**	Development (flower/seed/root); metabolic pathways; stress response; hormone response (ABA/C_2H_4)
bHLH	**(139)**	Development (trichome/root/carpel) abiotic stress; secondary metabolism; light responses;
MYB	**(190)**	Development; secondary metabolism; defence response; abiotic stress; hormone response (ABA/GA_3); cell cycle; light
C2H2(Zn)	**(112)**	Flower/seed development; abiotic stress; light
NAC	**(109)**	Development (meristem); auxin-response; virus resistance; *
HB	**(90)**	Development (several); sucrose signalling; cell death; *
MADS	**(82)**	Reproductive organs development; flowering time/abscission; *
bZIP	**(77)**	Flower/leaf/photomorphogenic development; seed-storage; defence response; hormone response/biosynthesis; *
WRKY	**(72)**	Defence response; *
C2C2(Zn)	**(104)**	Seed development/metabolism; flowering time; circadian rhythm; *

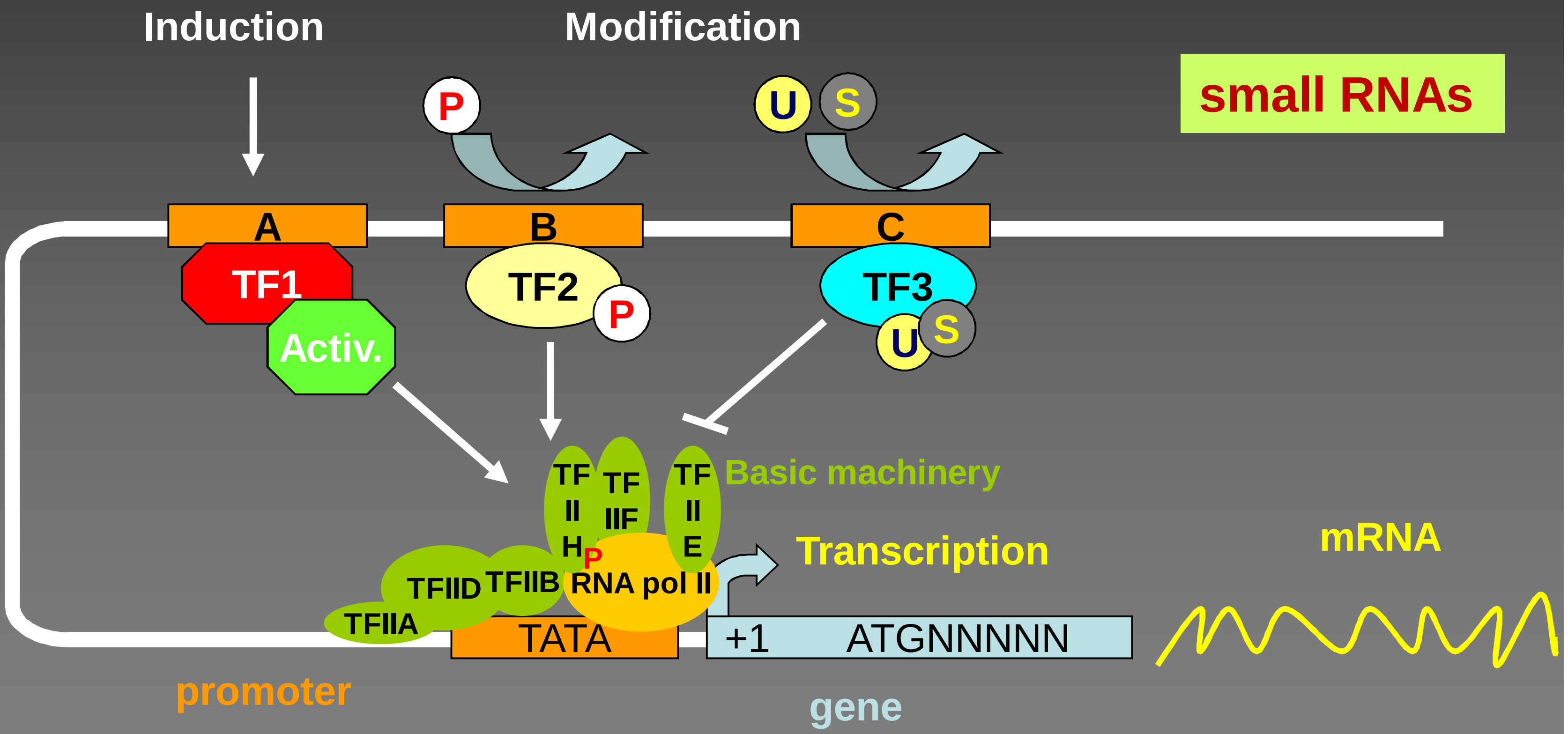
*** Abiotic stress**

Riechmann 2002 Transcriptional regulation: an overview. *The Arabidopsis Book*

Transcriptional regulatory network

Environmental stimuli

Developmental signals



Chromatin structure

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