InterTech

presents

Gene regulation

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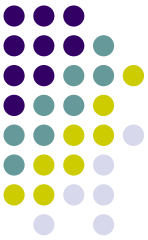
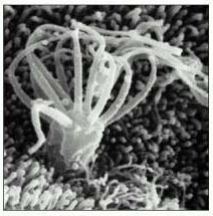


- DNA regulation
  - chromatin
  - gene and its surroundings
    - bacteria
    - eukarya
  - transcription factors
    - induction
    - repression
  - initiating transcription
- RNA regulation
  - RNA stability
  - interference RNA
  - transcription attenuation
    - *trp* operon
- Protein regulation
  - protein modifications
  - protein-protein interaction
    - activation
    - inhibition
  - cofactors
- Global regulatory mechanisms
  - sigma factor
  - SOS response

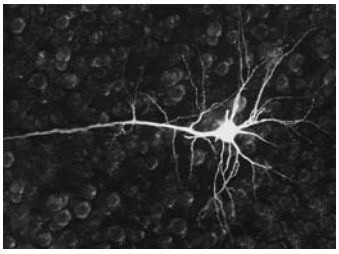
Gene regulation allows…

human embryo, R. Lanza, Advanced Cell Tecnology



Olfactory receptor neurons. (Alberts *et al*, 2002)

human neuron



DNA regulation

DNA regulation

- Chromatin
  - double helix accessibility

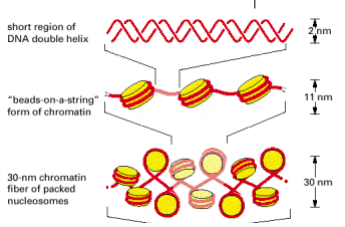


Figure 4-55. Chromatin packing (Alberts *et al*, 2002)

- Transcription factors
  - binding to the double helix

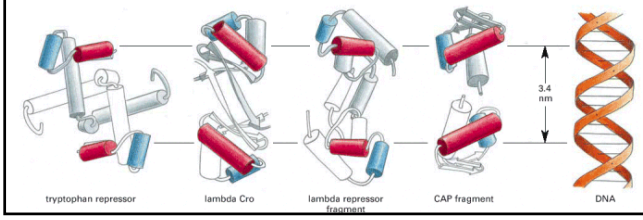


Figure 7-14. Some helix-turn-helix DNA-binding proteins. (Alberts *et al*, 2002)

chromatin

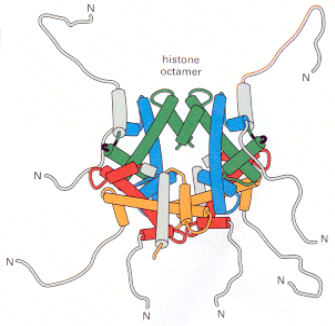


Figure 4-27. The assembly of a histone octamer. (Alberts *et al*, 2002)

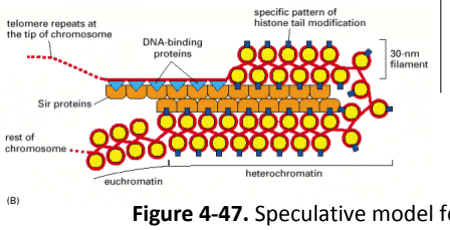
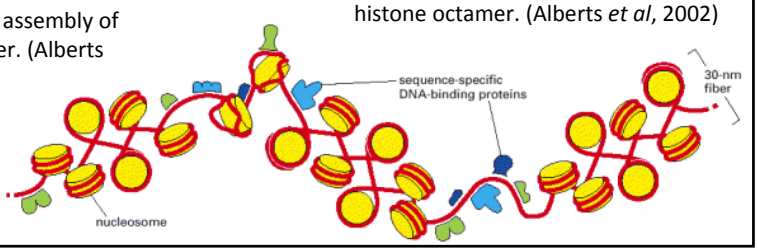


Figure 4-47. Speculative model for the heterochromatin at the ends of yeast chromosomes. (Alberts *et al*, 2002)

Figure 4-27. The assembly of a histone octamer. (Alberts *et al*, 2002)



chromatin

- Winding grades
  - Double helix –completely *opened*
  - Heterochromatin –completely *closed*
- physical barrier for transcription machinery

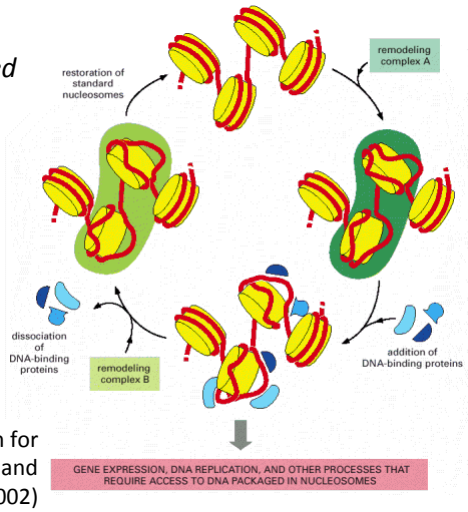
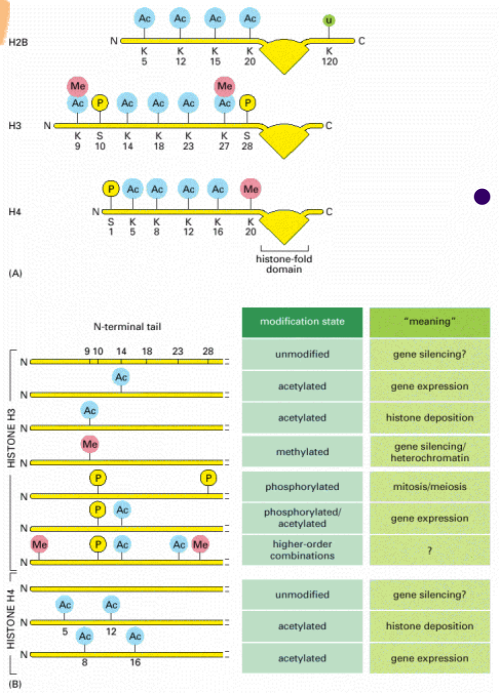


Figure 4-34. A cyclic mechanism for nucleosome disruption and reformation. (Alberts *et al*, 2002)



- Histone code
  - really a code ?
  - traffic lights *are* code

Figure 4-35. Covalent modification of core histone tails. (Alberts *et al*, 2002)

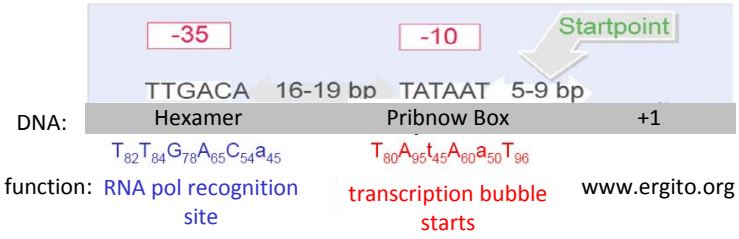
transcription factors

- proteins that bind to a promoter region
- promoter : regulatory region upstream a gene

let's take a closer look to a promoter before…

gene and its surroundings : bacteria

- Promoter/Operator



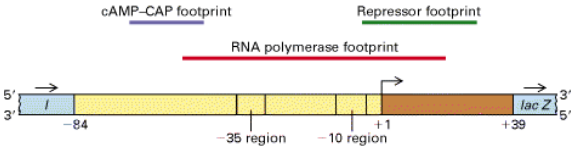


Figure 10-9. Diagram of the *lac* operon transcription control region. (Lodish *et al*, 2000)

gene and its surroundings : eukarya

- Promoter + enhancing region

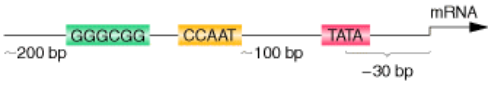
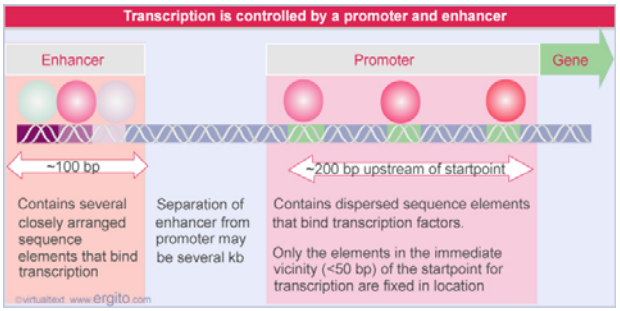


Figure 14-19. The promoter region in higher eukaryotes. (Griffiths *et al*, 2000)



Gene regulation

genes organization: bacteria vs. eukarya

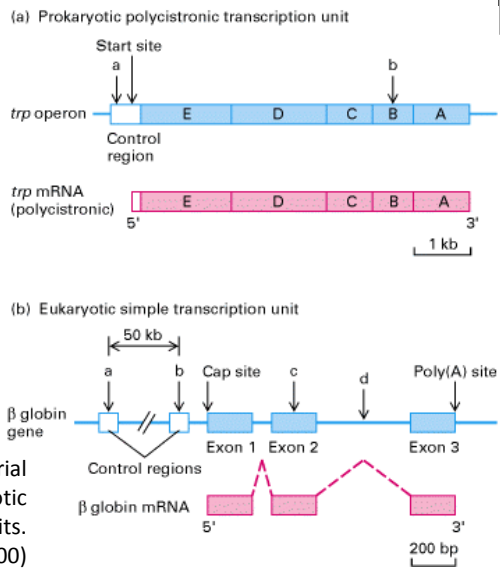


Figure 9-1. Comparison of bacterial operons and simple eukaryotic transcription units. (Lodish *et al*, 2000)

transcription factors

- proteins
- different functional domains
  - DNA binding
  - protein interaction
  - catalytic

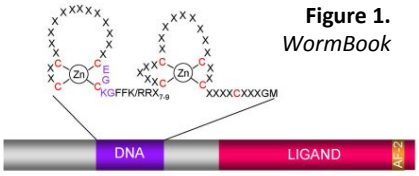


Figure 1. *WormBook*

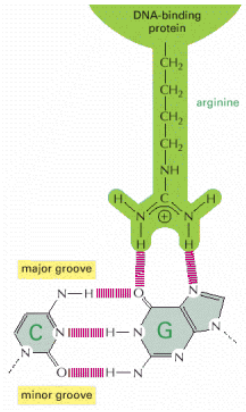
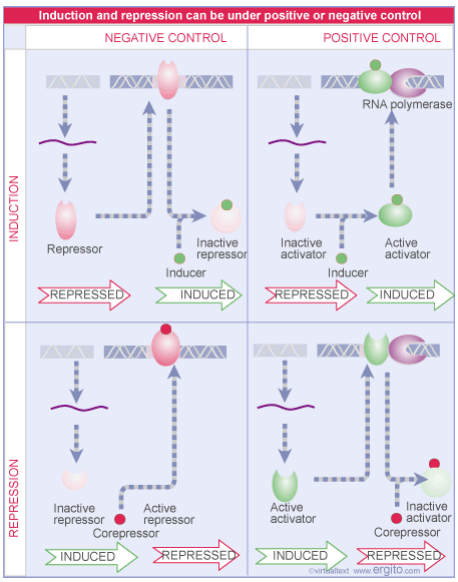


Figure 7-27. One of the most common protein-DNA interactions. (Alberts *et al*, 2002)

gene regulation overview

negative control: TF inhibits

positive control: TF activates

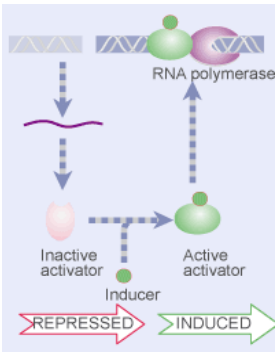


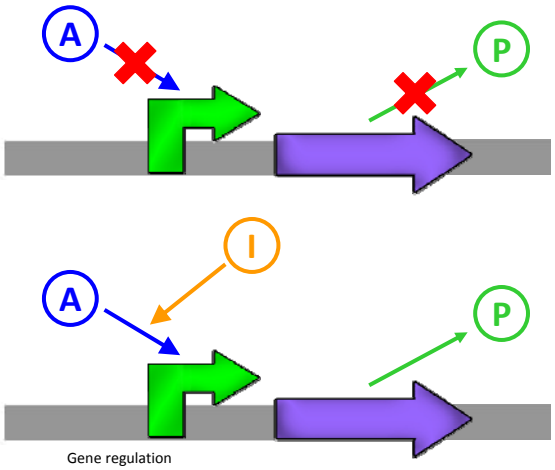
induction: gene ends up expressed

repression: gene ends up silenced

transcription factors

- induction : positive control

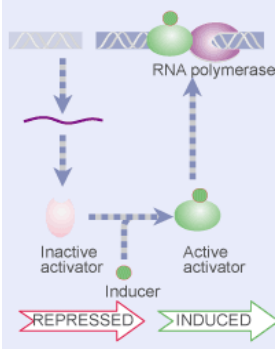




Gene regulation

transcription factors

- induction : positive control
  - cell signalling : steroid hormones



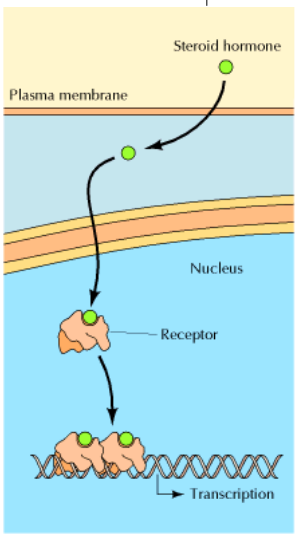


Figure 13.3. Action of steroid hormones (Cooper, 2000)

transcription factors

- thyroid hormone

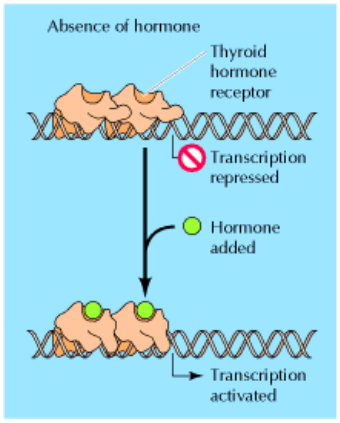
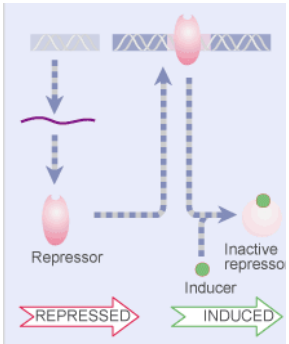
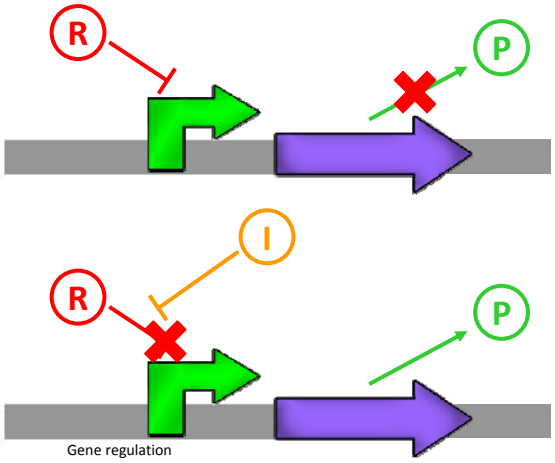


Figure 13.4. Gene regulation by the thyroid hormone receptor (Cooper, 2000)

transcription factors

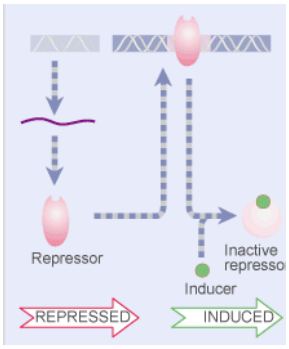
- induction : negative control

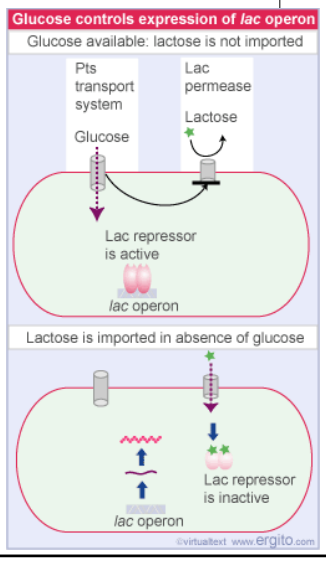




transcription factors

- induction : negative control
  - *lac* operon

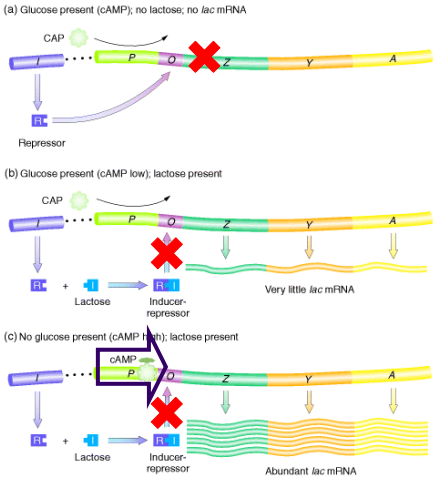




Gene regulation

transcription factors

- *lac* operon



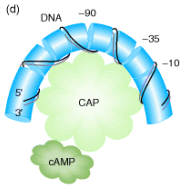
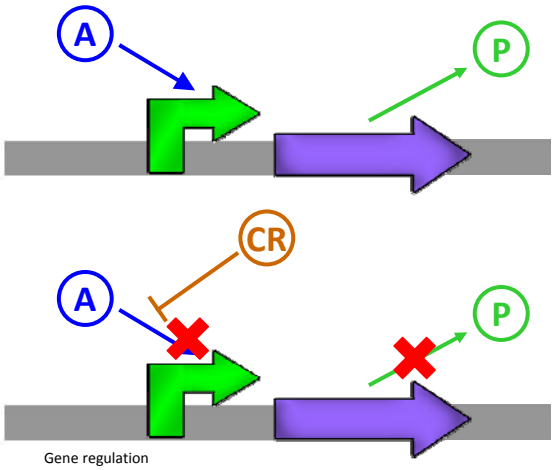


Figure 14-14. Negative and positive control of the *lac* operon by the Lac repressor and catabolite activator protein (CAP), respectively. (Griffiths *et al*, 2000)

transcription factors

- repression : positive control



Gene regulation

transcription factors

- repression : positive control
  - Rb protein and cell cycle

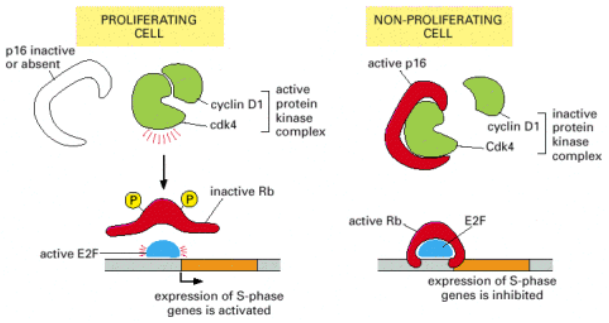
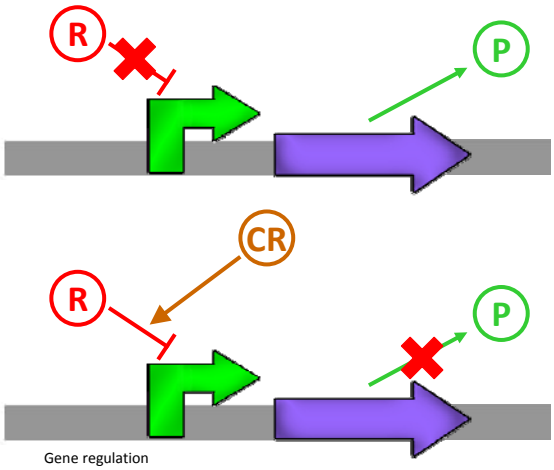


Figure 23-32. The pathway that controls cell cycling via Rb protein. (Alberts *et al*, 2002)

transcription factors

- repression : negative control



transcription factors

- repression : negative control
  - *trp* repressor + *trp*

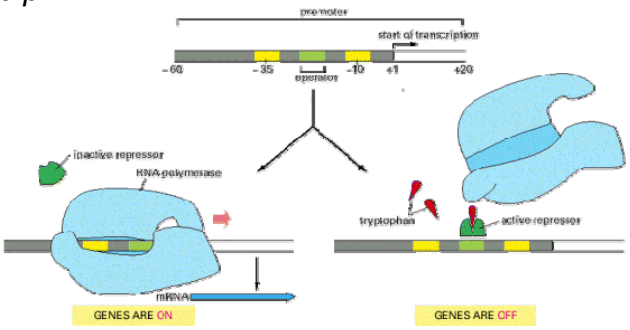


Figure 7-34. Switching the tryptophan genes on and off. (Alberts *et al*, 2002)

initiating transcription : overview

- physical barriers : allow transcription
- integration of signals : positive
- not an on / off behaviour : continuous levels

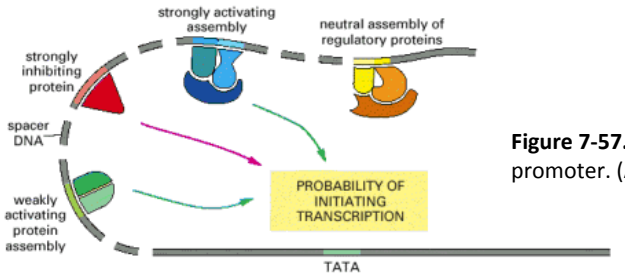
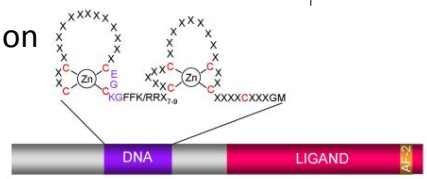


Figure 7-57. Integration at a promoter. (Alberts *et al*, 2002)

initiating transcription : overview

- proteins have a coordinated action
- signalling is a key player
  - integration of signals
- combination of regulation types
  - complexity through combination



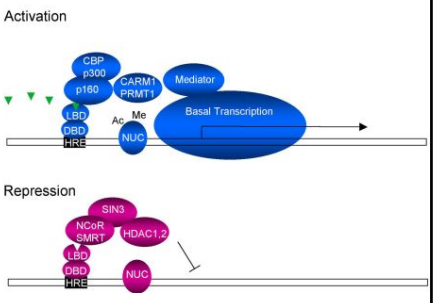


Figure 1. *WormBook*

RNA regulation

RNA regulation

- RNA stability
- interference RNA
- transcription attenuation
  - *trp* operon

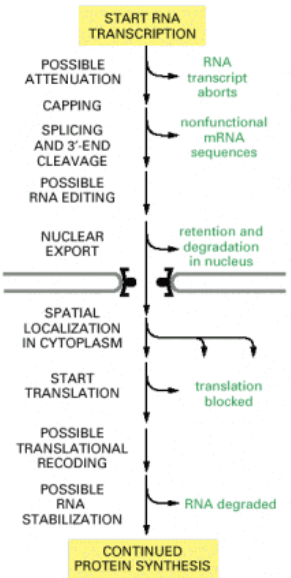


Figure 7-87. Possible post-transcriptional controls on gene expression. (Alberts *et al*, 2002)

RNA stability

- check for errors
- repair or degrade

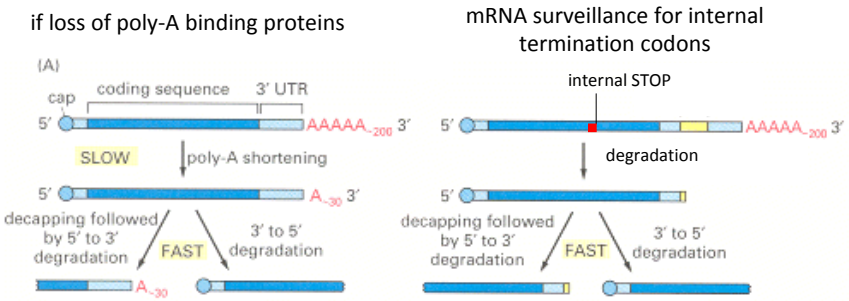
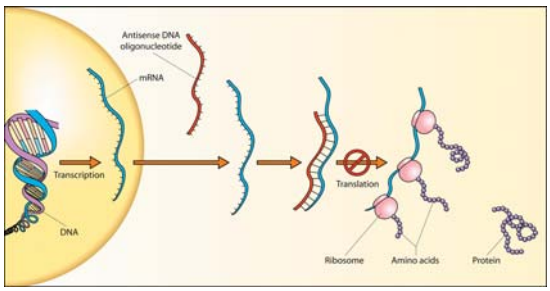


Figure 7-103. Two mechanisms of eucaryotic mRNA decay. (Alberts *et al*, 2002)

interference RNA

- eukaryotic defense
- degrades dsRNA
  - mainly virus genome
  - evolutionary mechanism !
- widely used in genetic engineering



interference RNA

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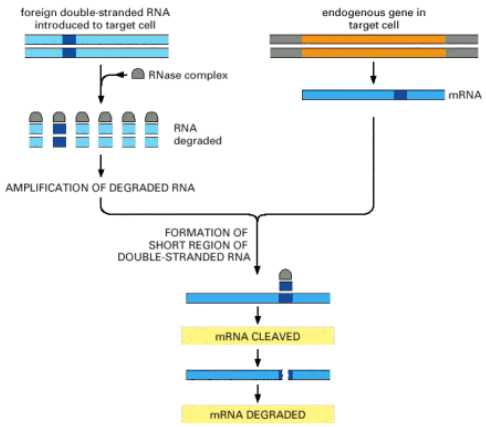
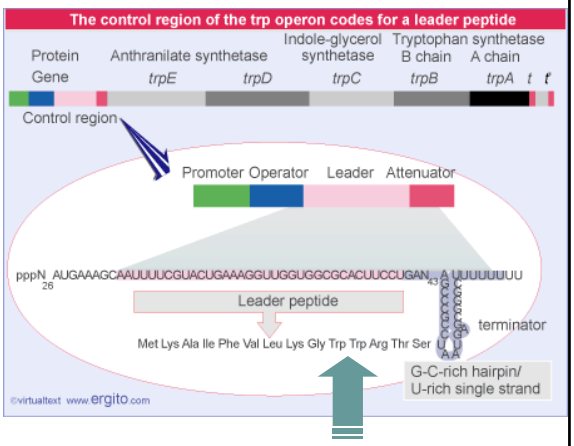


Figure 7-107. The mechanism of RNA interference. (Alberts *et al*, 2002)

transcription attenuation : *trp* operon

- already has a *trp* repressor
- codes for proteins that produce tryptophan, an amino acid
- attenuation
  - 2ary mechanism
  - provides fine control
  - controls translation



transcription and translation : prokaryote vs eukaryote

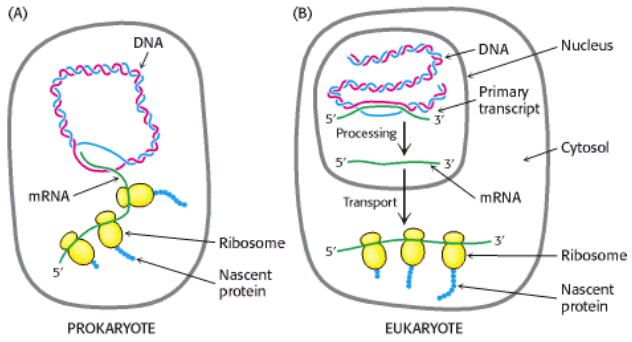


Figure 28.15. Transcription and Translation. (Berg *et al*, 2002)

transcription attenuation : *trp* operon

- sequence 3
  - with low *trp*, binds to 2
  - with high *trp*, binds to 4
- if sequences 2 & 3 bind
  - then transcription continues ☑
- if sequences 3 & 4 bind
  - then transcription terminates ☒

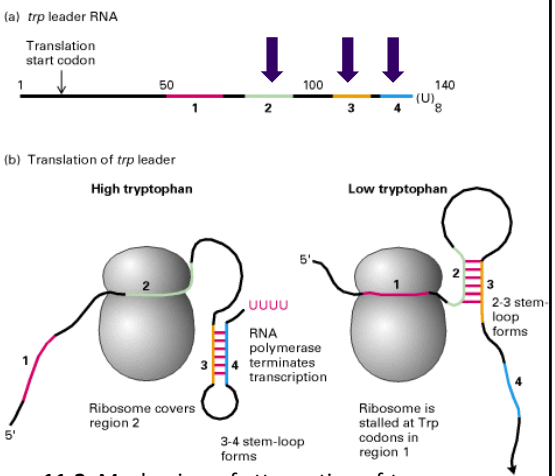


Figure 11-3. Mechanism of attenuation of *trp* operon transcription. (Lodish *et al*, 2000)

protein regulation

protein regulation

- protein modifications
- protein-protein interaction
  - activation
  - inhibition
- cofactors

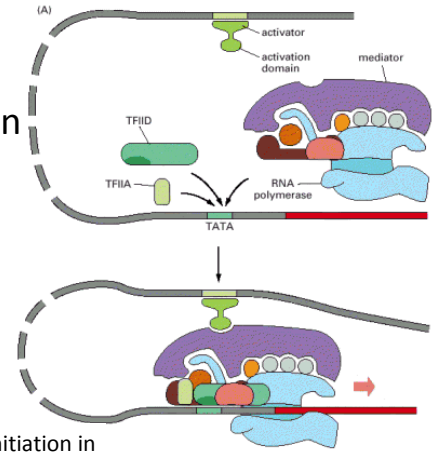


Figure 7-43. Activation of transcription initiation in eucaryotes by recruitment of the eucaryotic RNA polymerase II holoenzyme complex. (Alberts *et al*, 2002)

protein modifications

- phosphorylation
- one major protein modification
  - activation
  - Inhibition
- others
  - acetilation
  - metilation
  - glycosylation
  - attachment of lipids

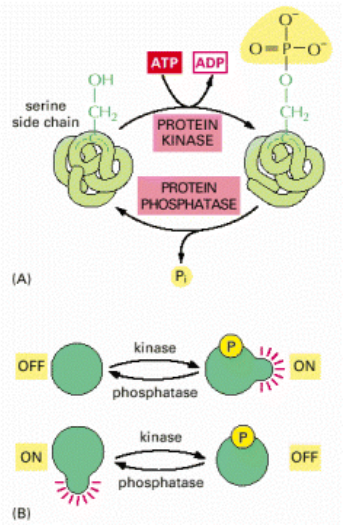


Figure 3-63. Protein phosphorylation. (Alberts *et al*, 2002)

protein-protein interaction

- activation
  - interaction of protein subunits causes gain of function
- example
  - *coordination* of transcription factors

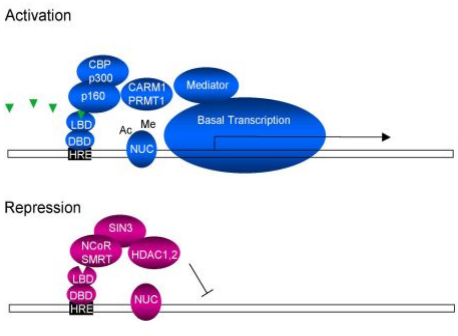


Figure 1. *WormBook*

protein-protein interaction

- inhibition
  - interaction of protein causes lost of function
- example
  - subunits of cAMP-dependent kinase

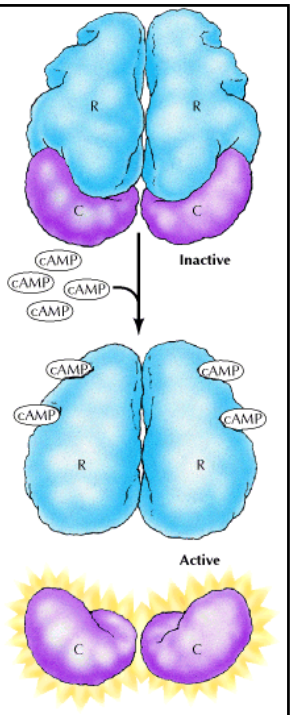


Figure 7.38. Regulation of cAMP-dependent protein kinase. (Alberts et al, 2002)

cofactors

- adds functional groups to a reaction
- permits protein to catalyse a given reaction
- examples
  - Fe at heme group in hemoglobin
  - Zn^{2+} at Zinc finger domain
  - NAD^+, FAD^+, $NADP^+$ at redox reactions
- synthesised or eaten (vitamins)

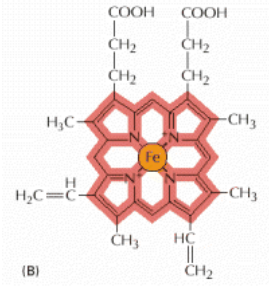


Figure 3-53. Retinal and heme. (Alberts *et al*, 2002)

Global regulatory mechanisms

- sigma factor
- SOS response

sigma factor

SIGMA FACTOR	PROMOTERS RECOGNIZED
σ^{70}	most genes
σ^{32}	genes induced by heat shock
σ^{28}	genes for stationary phase and stress response
σ^{28}	genes involved in motility and chemotaxis
σ^{54}	genes for nitrogen metabolism

Table 7-2. Sigma Factors of *E. coli*. (Alberts *et al*, 2002)

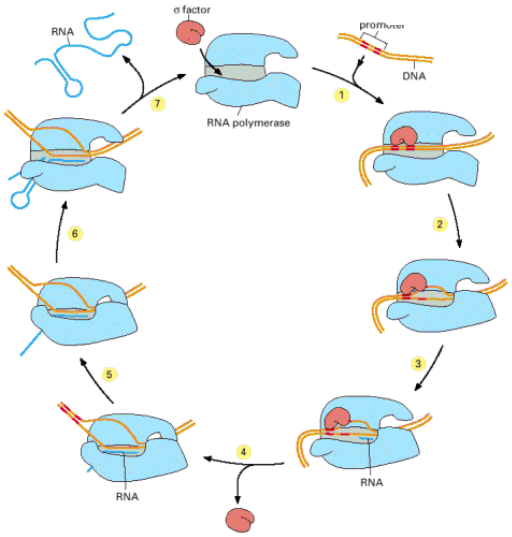


Figure 6-10. The transcription cycle of bacterial RNA polymerase. (Alberts *et al*, 2002)

sigma factor : heat shock

- caused when temperature > 40 ºC
- triggers abundant σ^{32}
  - transcribes a huge set of genes → heat shock proteins (*hsp*)
- function : survival in suboptimum temperature
  - *hsp* prevents cell from dying
  - *hsp* keeps protein from being unfold
- *hsp* are proteins widespread in all organisms

SOS response in *E. coli*

- caused when replication is blocked
  - drastic change in environment
- excess single strand DNA triggers active RecA
  - unblocks ≈15 genes
- function : survival in altered environment
  - increases cell survival after DNA damage
  - copies genome, even error-prone
    - harmful for a single bacterial cell
    - burst of genetic variability, chance of a surviving mutant

sources

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