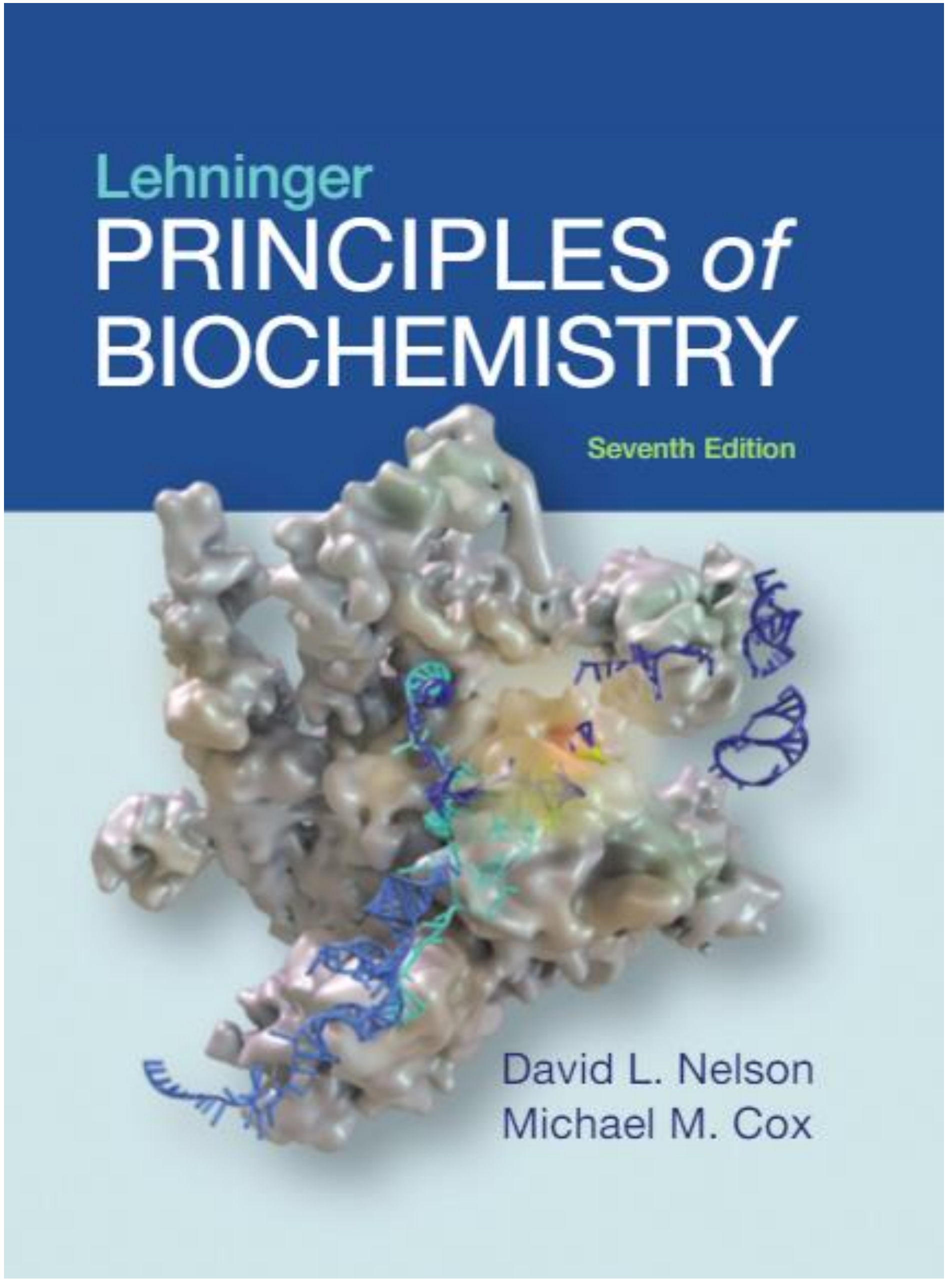
28 | Regulation of Gene Expression



Ways to Regulate Protein Concentration in a Cell

- Synthesis of primary RNA transcript
- How to process this RNA into mRNA
- Posttranscriptional modifications of mRNA
- Degradation of mRNA
- Protein synthesis
- Posttranslational modification of protein
- Targeting and transport of the protein
- Degradation of the protein
- **Seven Processes That Affect the Steady-State Concentration of a Protein**

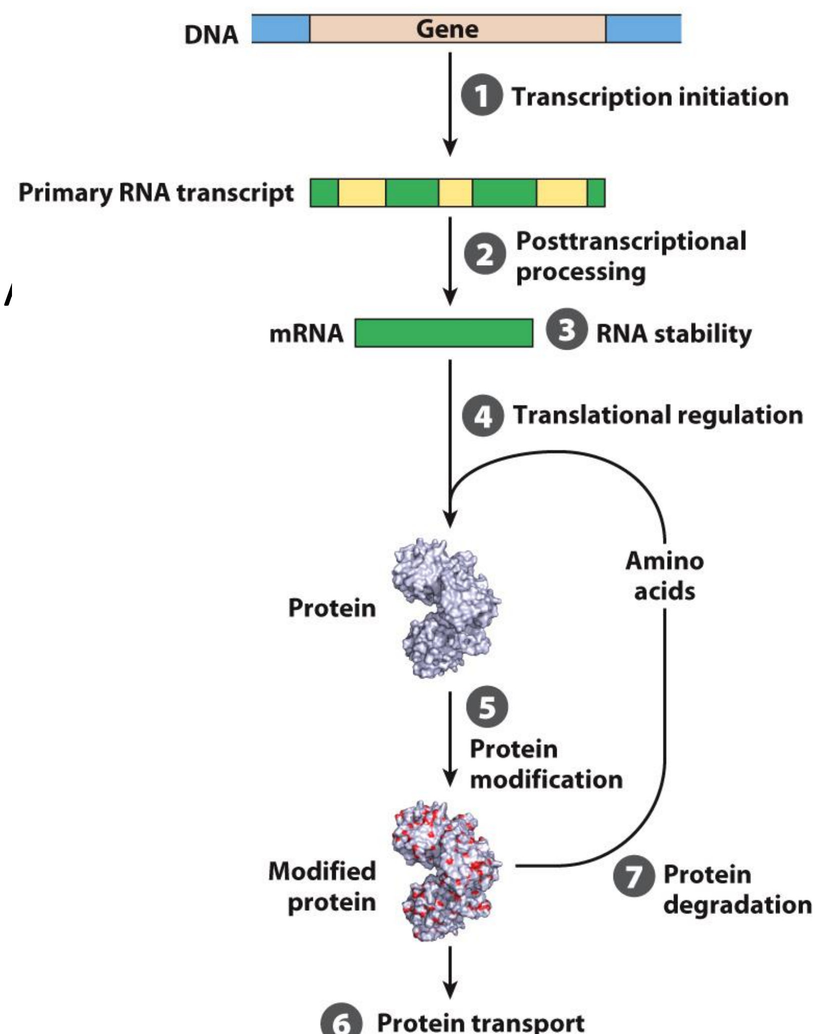


Figure 28-1
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The Vocabulary of Gene Regulation

- **Housekeeping gene**
  - under constitutive expression
  - constantly expressed in approximately all cells
- **Regulated gene**
  - Levels of the gene product rise and fall with the needs of the organism.
  - Such genes are **inducible.**
    - able to be turned on
  - Such genes are also **repressible**.
    - able to be turned off

Small-Molecule Effectors Can Regulate Activators and Repressors

- **Repressors** reduce RNA Pol-promoter interactions or block the polymerase.
  - bind to operator sequences on DNA
    - usually near a promoter in bacteria but further away in many eukaryotes
- **Effectors** can bind to repressor and induce a conformational change.
  - change may increase or decrease repressor’s affinity for the operator and thus may increase or decrease transcription

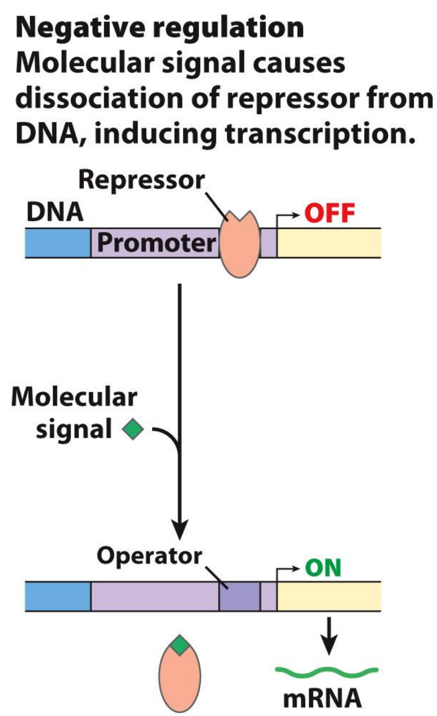
Activators Improve Contacts Between RNA Polymerase and the Promoter

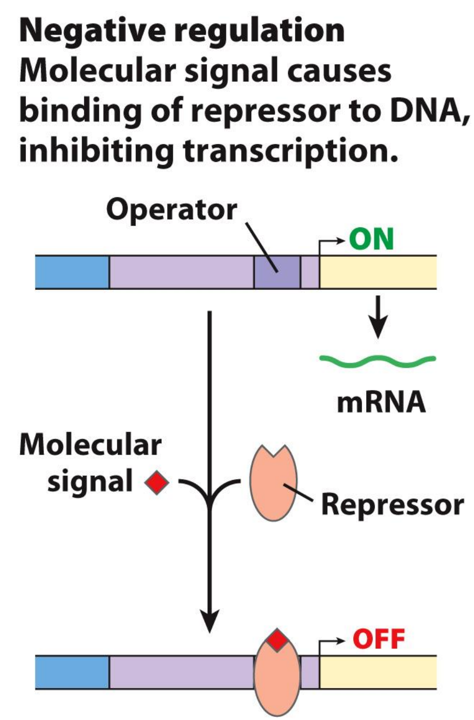
- Binding sites in DNA for activators are called enhancers.
- In bacteria, enhancers are usually adjacent to the promoter.
  - often adjacent to promoters that are “weak” (bind RNA polymerase weakly), so the activator is necessary
- In eukaryotes, enhancers may be very distant from the promoter.

Negative Regulation

- Negative regulation involves **repressors.**
  - Example: Repressor binds to DNA and shuts down transcription
  - Alternative: Signal causes repressor to dissociate from DNA; transcription induced

Despite opposite effects on transcription, both are negative regulation





Positive Regulation

- Positive regulation involves **activators.**
- Enhance activity of RNA polymerase
  - Activator-binding sites are near promoters that weakly bind RNA Pol or do not bind at all.
  - It may remain bound until a molecule signals dissociation.
  - Alternatively, the activator may only bind when signaled.

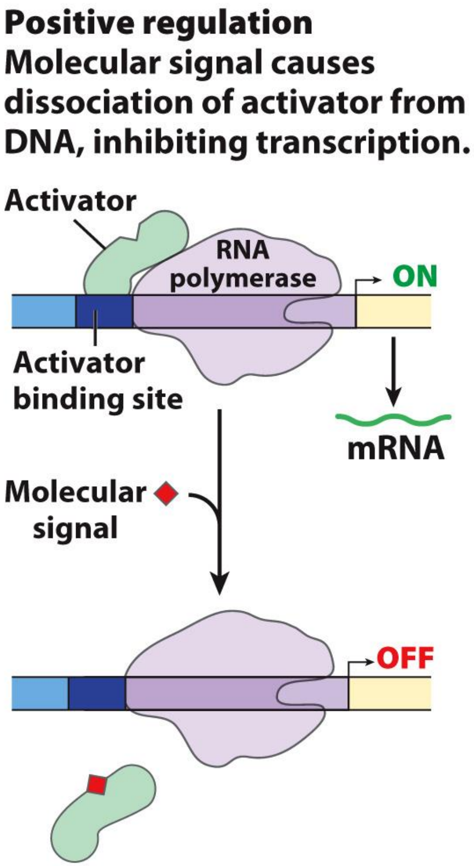


Figure 28-4c
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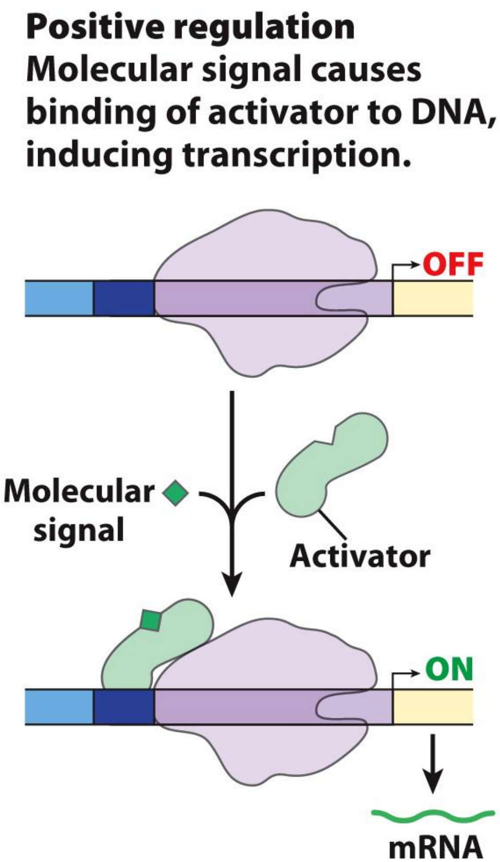

Figure 28-4d
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DNA Looping Allows Eukaryotic Enhancers to Be Far from Promoters

- Activators can influence transcription at promoters thousands of bp away.
- How? Via formation of DNA loops
- Looping can be facilitated by **architectural regulator proteins.**
- **Co-activators** may mediate binding by binding to both activator and RNA polymerase.

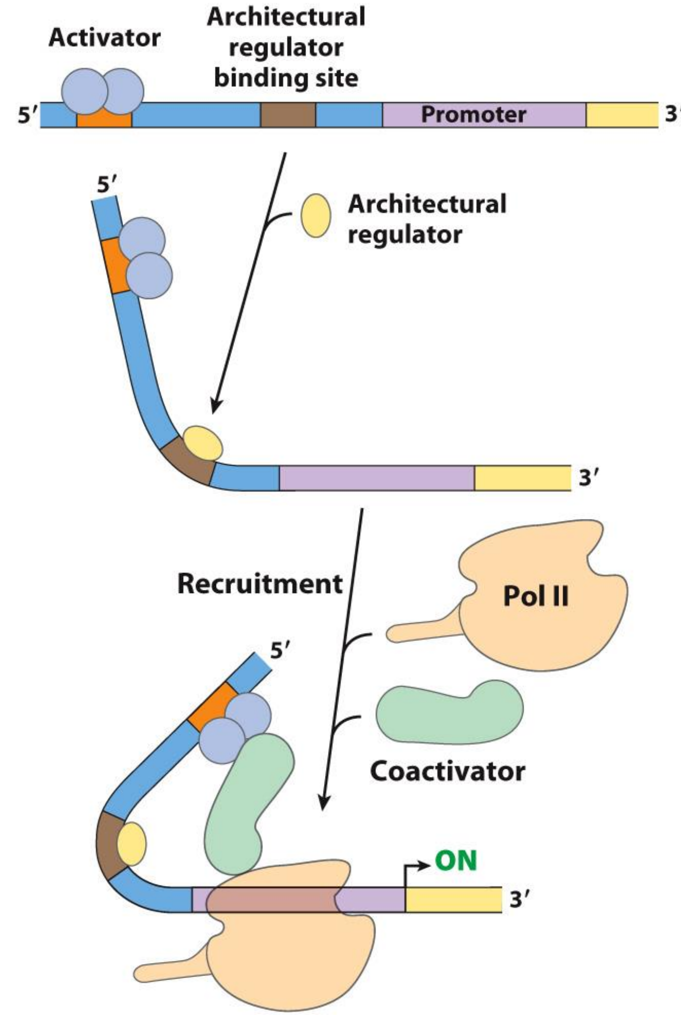

Figure 28-5
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Many Bacterial Genes Are Transcribed And Regulated Together in an Operon

- An operon is a cluster of genes sharing a promoter and regulatory sequences.
  - Genes are transcribed together, so mRNAs are several genes represented on one mRNA (polycistronic).
- First example: the *lac* operon

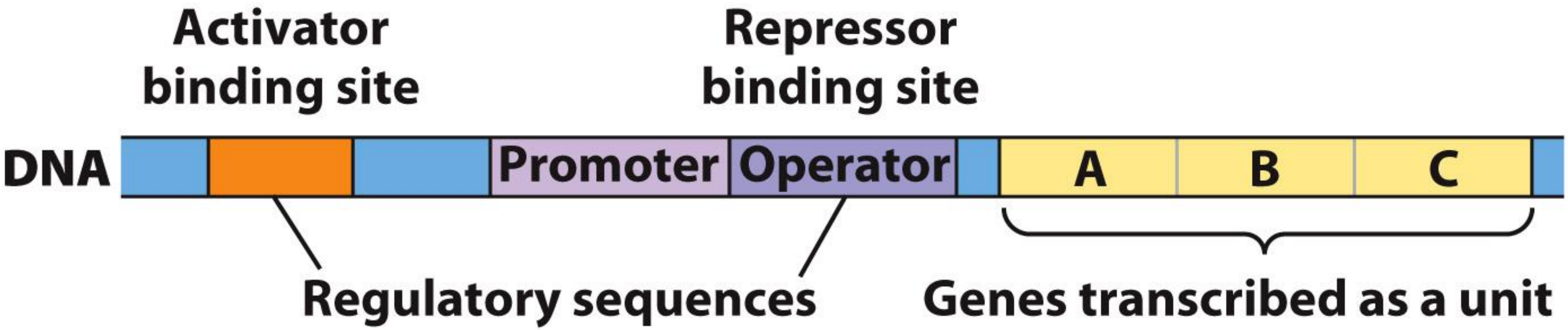

Figure 28-6
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The *lac* Operon Reveals Many Principles of Gene Regulation

- Work of Jacob and Monod – 1960
- Shows how three genes for metabolism of lactose are regulated together as an operon:
  - β-galactosidase (lacZ)
    - cleaves lactose to yield glucose and galactose
  - lactose permease (galactoside permease; lacY)
    - transports lactose into cell
  - thiogalactoside transacetylase (lacA)
- Rely on negative regulation via a repressor.

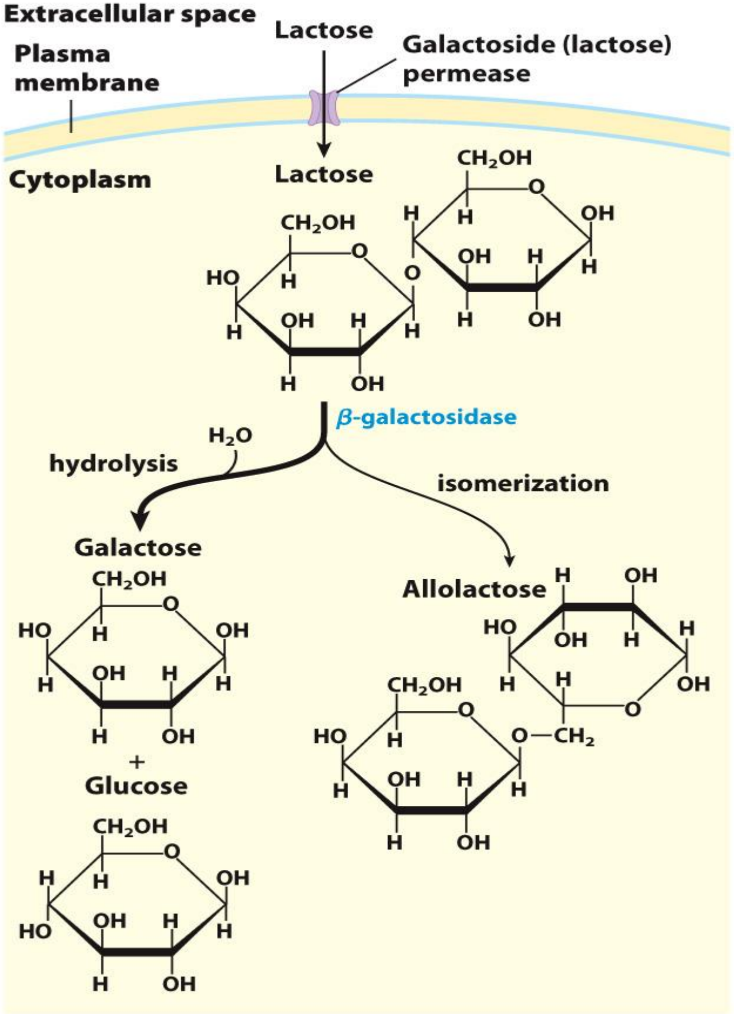

Figure 28-7
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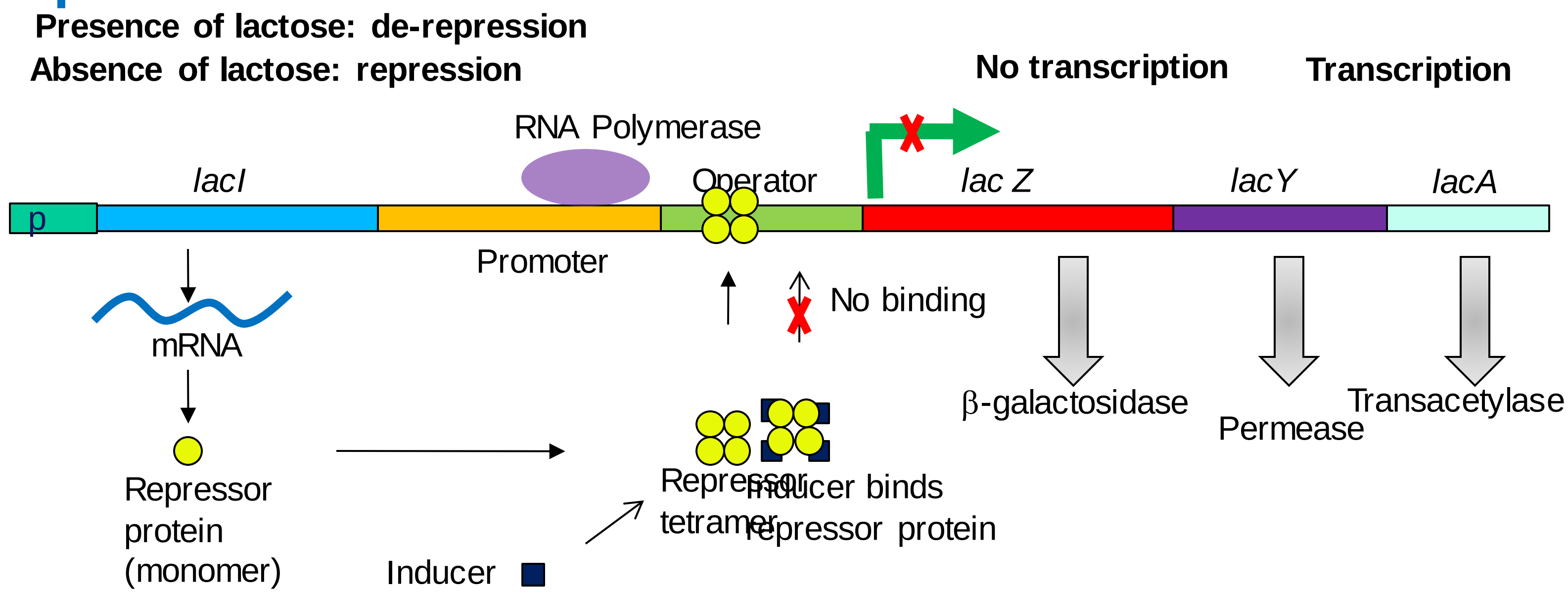
Lactose Metabolism in *E. Coli*

- When glucose is abundant and lactose is lacking, cells make only very low levels *of enzymes for lactose metabolism.*
  - **Transcription is *repressed*.**
- If glucose is scarce and cells are fed lactose, the cells can use it as their energy source.
- The cells suddenly express the genes for the enzymes for lactose metabolism.
  - ***Transcription is no longer repressed.***

The *lac* operon: negative control by *lacI* repressor



Inhibiting the Transcription of the *lac* Operon via a Repressor Protein

- A gene called *lacI* encodes a repressor called the Lac repressor.
  - It has its own promoter P_I.
    - Transcription of the repressor is independent of transcription of the enzymes the repressor regulates.
  - The repressor can bind to three operator sites (O_1–O_3).
- The Lac repressor binds primarily to the operator O_1.
  - O_1 is adjacent to the promoter.
  - Binding of the repressor helps prevent RNA polymerase from binding to the promoter.
- The repressor also binds to one of two secondary operators, with the DNA looped between this secondary operator and O_1 (see Fig. 28-8b).

It reduces transcription, but ***transcription occurs at a low, basal rate,*** even with the repressor bound.

Structure of the *lac* Operon

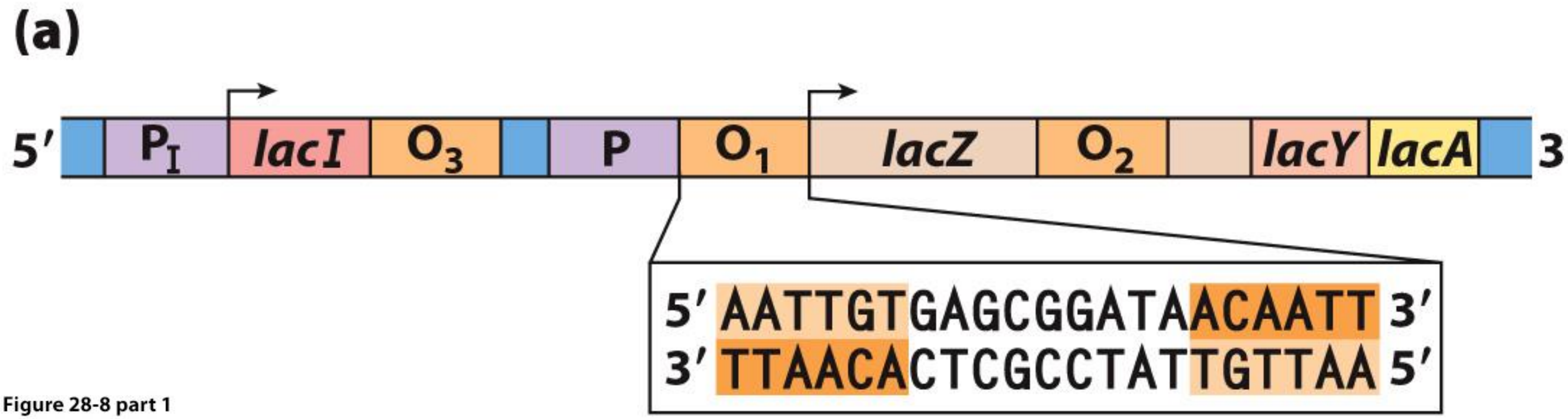


Figure 28-8 part 1
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Lac Repressor Bound to O_1 and O_3 with DNA Looped Between

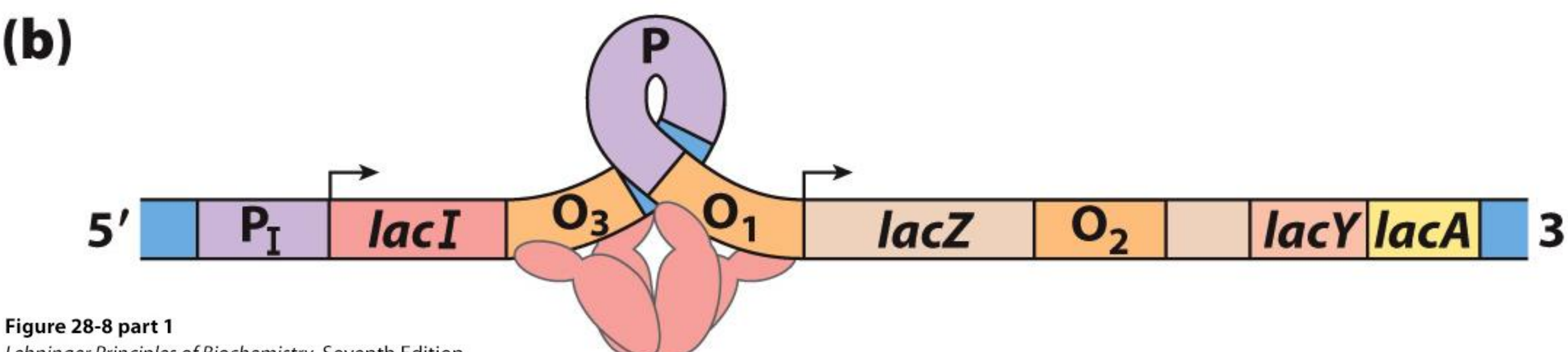

Figure 28-8 part 1
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How Lac Repressor Binds to DNA

- Lac repressor is a tetramer.
  - dimer of dimers
  - Each dimer binds to the palindromic operator sequence.
- The O_1 sequence reflects the symmetry of the repressor.
- There are approximately 20 repressors per cell.

The *lac* Operon Is Governed by More Than Repressor Binding

- The availability of glucose governs expression of lactose-digesting genes via **catabolite repression.**
  - When glucose is present, lactose genes are turned off.
  - It is mediated by cAMP and cAMP receptor protein (CRP or CAP for catabolite activator protein).

When Glucose Is Absent, *lac* Operon Transcription Is Stimulated by CRP-cAMP

- cAMP binds near the promoter.
  - stimulates transcription 50-fold
  - bends DNA
  - open complex doesn't form readily without CRP-cAMP
- CRP-cAMP only has this effect when the Lac repressor has dissociated.
- cAMP is made when [glucose] is low.

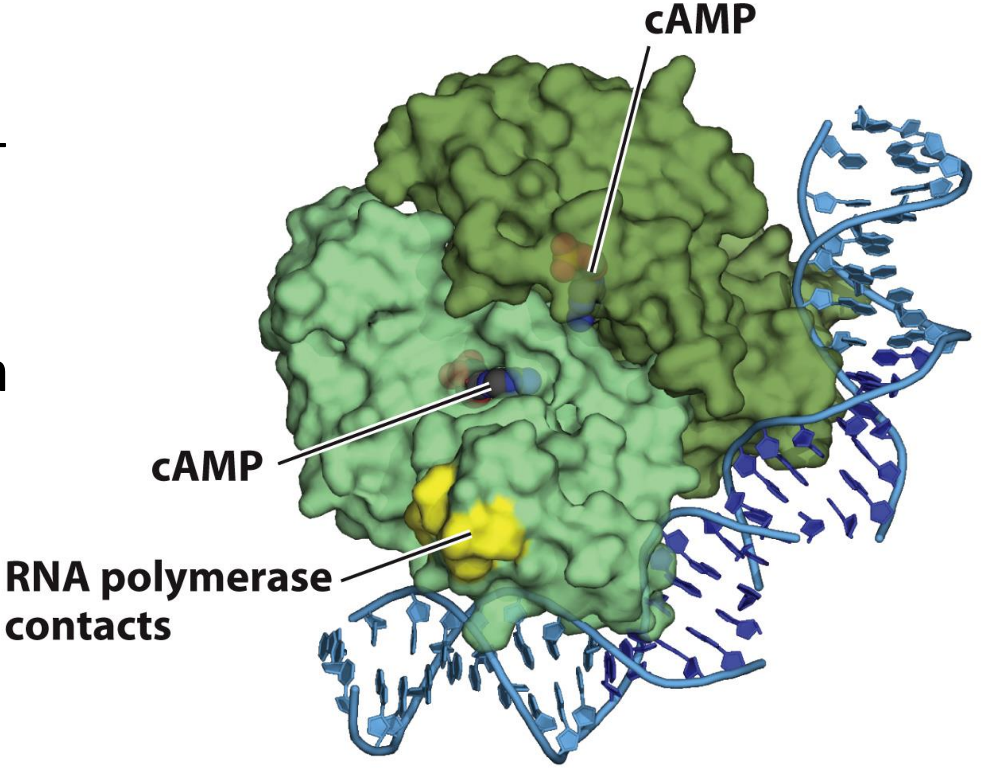

Figure 28-17
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When Lactose Is Absent
Little to No Transcription Occurs

Whether [glucose] is high or low, if lactose is absent → repressor stays bound….→ no transcription even when CRP-cAMP bind.

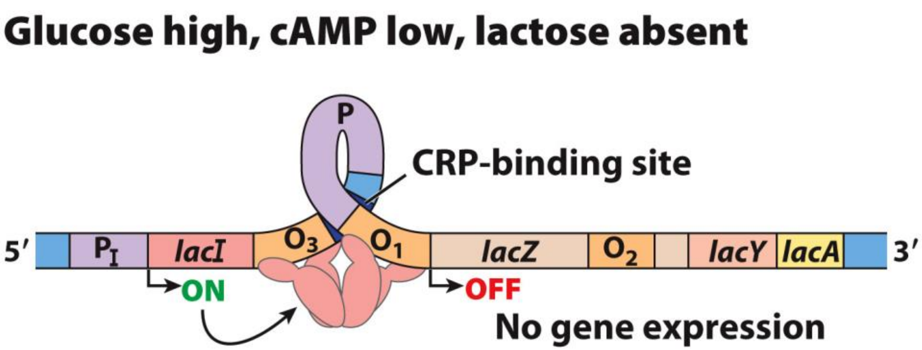

Figure 28-18a
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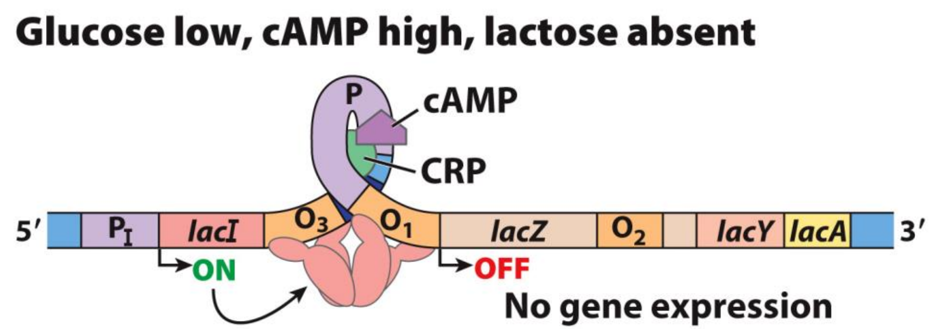

Figure 28-18b
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When Lactose Is Present, Transcription Depends On Glucose Level

- Repressor dissociates, but transcription is only stimulated significantly if cAMP rises.

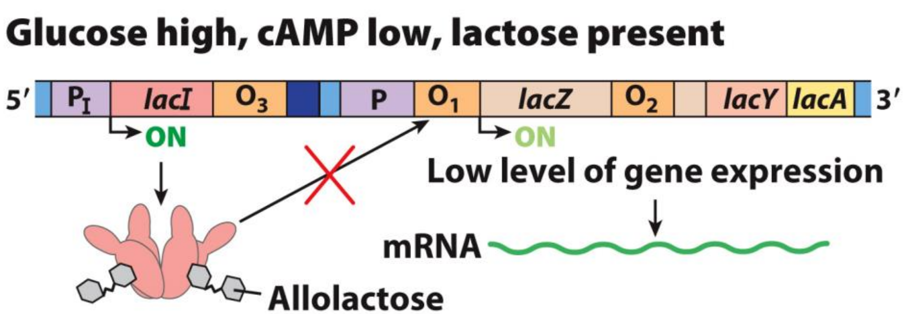

Figure 28-18c
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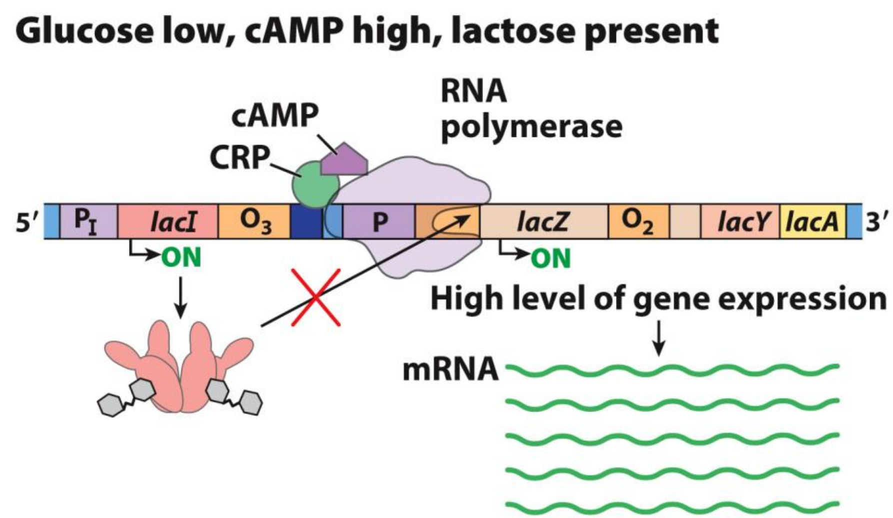

Figure 28-18d
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Two Requirements for Strongest Induction of the *lac* Operon

1. Lactose must be present to form allolactose to bind to the repressor and cause it to dissociate from the operator.
   - reducing repression
2. [Glucose] must be low so that cAMP can increase, bind to CRP, and the complex can bind near the promoter
   - causing activation

Combined Effects of Glucose and Lactose on the *lac* Operon

- When lactose is low, repressor is bound:
  →inhibition
- When lactose is high, repressor dissociates
  →permitting transcription
- When glucose is high, CRP is not bound and
  →transcription is dampened
- When glucose is low, cAMP is high and CRP is bound
  →activation

The *trp* Operon

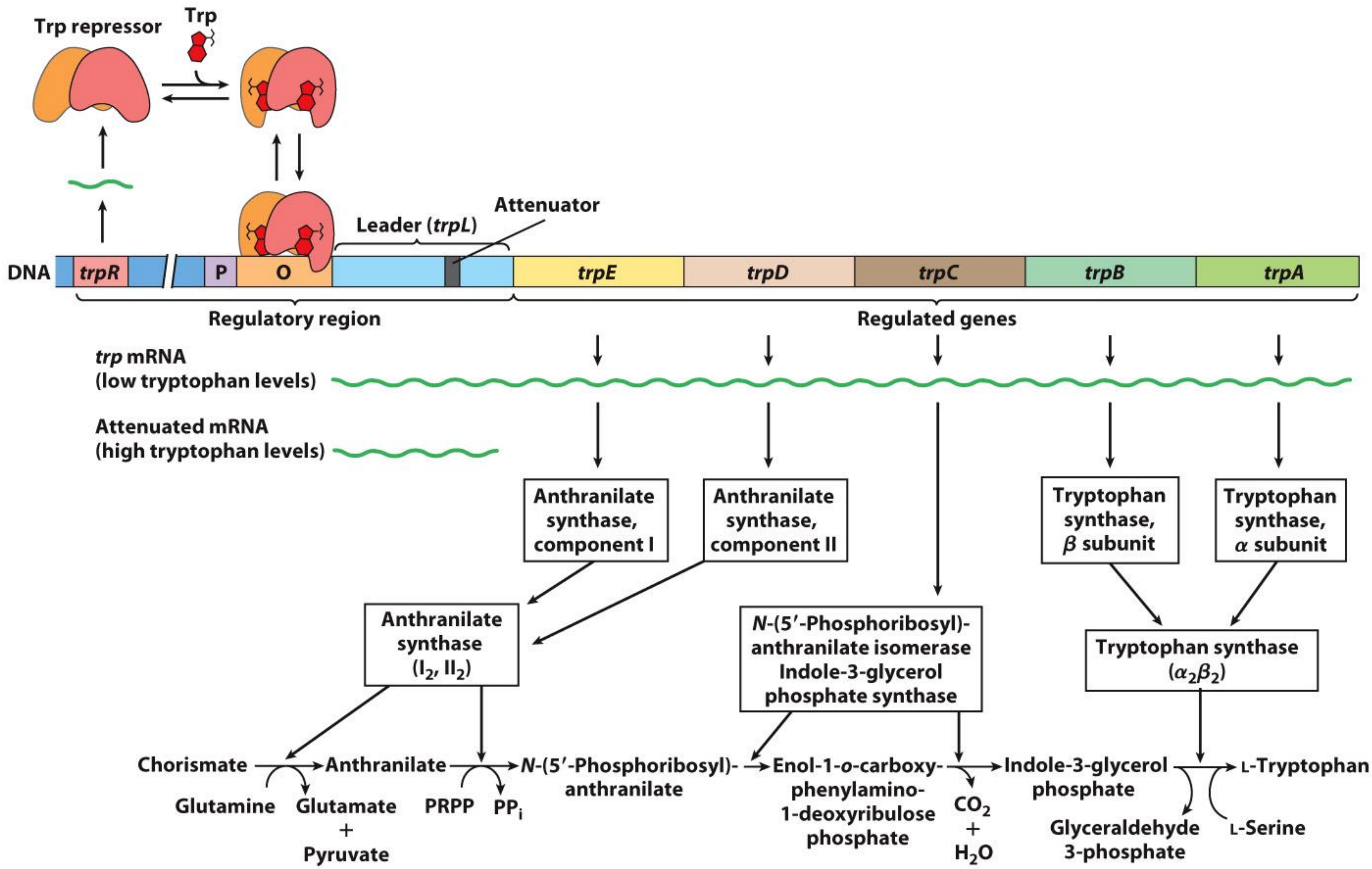

Figure 28-19
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