Regulation of Gene expression (I)

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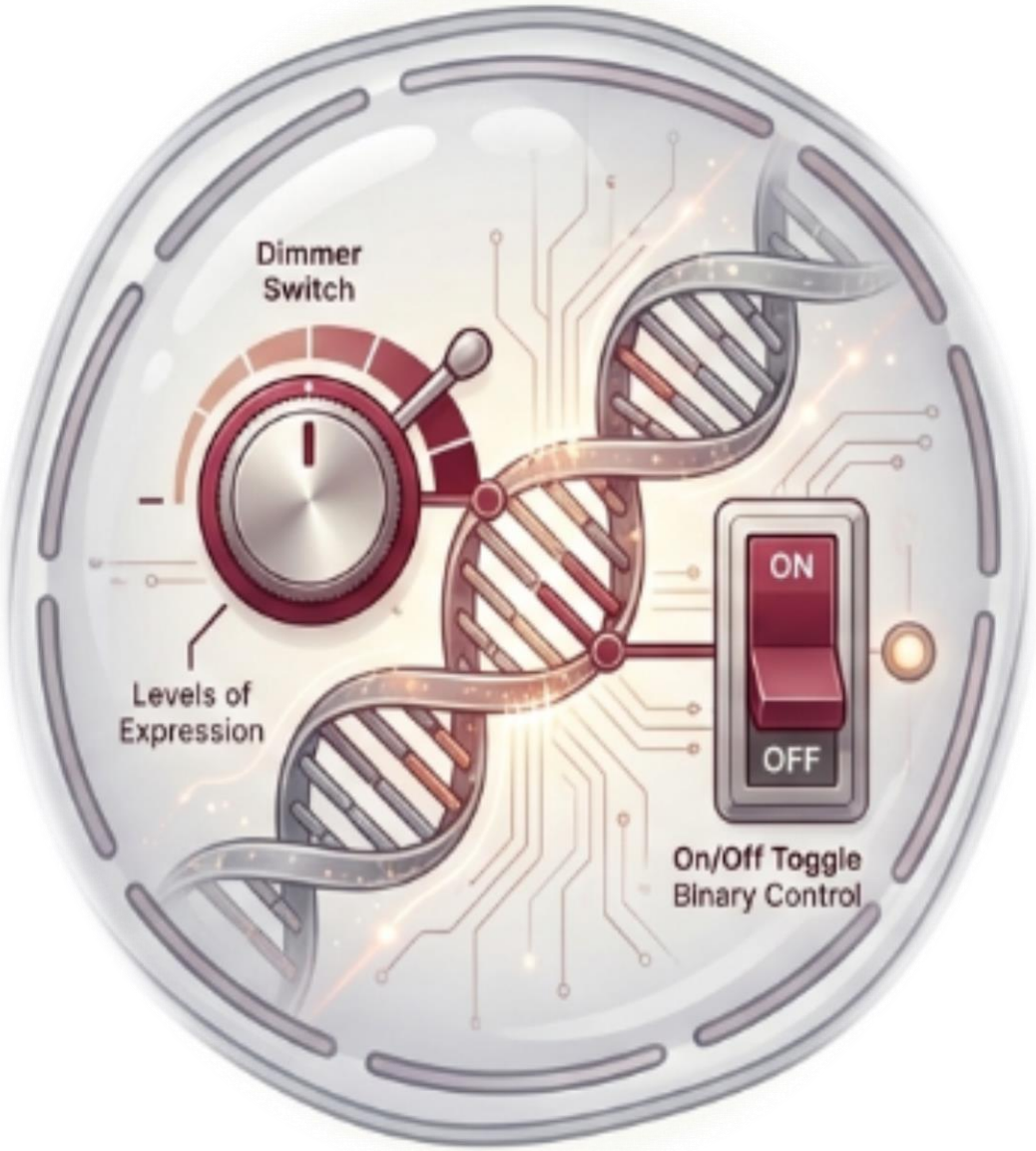


Every cell holds the same manual. Regulation decides which pages are read.

Learning outcomes

By the end of lecture, students should be able to:

- Identify the concept of regulation of gene expression
- Explain the difference between constitutive (housekeeping) expression and inducible/repressible systems
- Describe operon structural genes & control (regulatory) molecules.
- Compare inducible operons and repressible operons
- Recognize why regulation of operons is important.

Case Scenario

- 20-year-old female patient presents to the dental clinic complaining of: increased tooth sensitivity & visible white and brown spots on her teeth. On history taking: she consumes sugary snacks and soft drinks frequently throughout the day & oral hygiene is irregular. Clinical examination reveals early enamel demineralization & Plaque accumulation on tooth surfaces. Salivary analysis shows high levels of *Streptococcus mutans*.
- **How does frequent sugar intake affect bacterial gene expression?**
- **Which operon model explains this situation best?**

Introduction

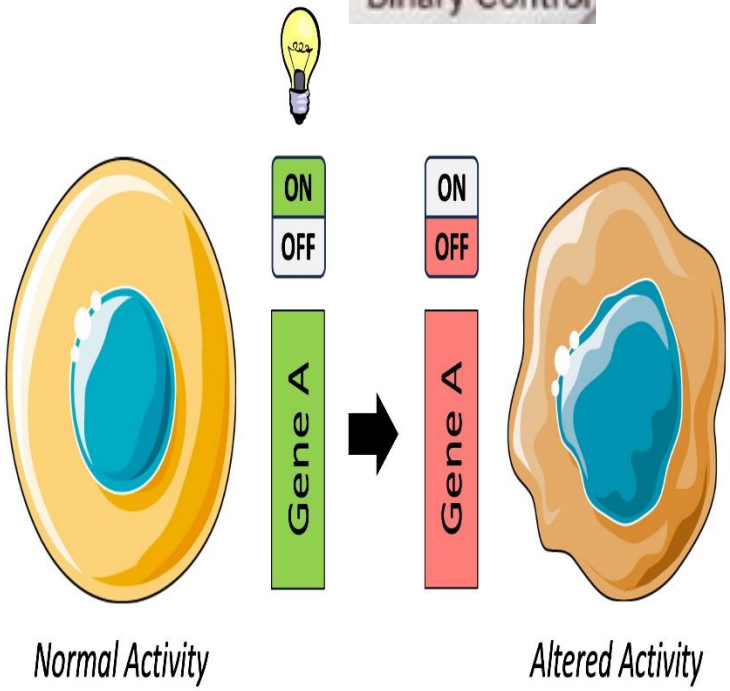
- Each nucleated cell in a multicellular organism contains copies of the same DNA.
- If each cell in a multicellular organism has the same DNA, then how is that cells in different parts of the organism's body exhibit different characteristics??

Regulation of gene expression

- The relationship between genes and their effects is complex.
- Despite the uniquity of the genetic code, each genetically identical cell does not turn on "express" the same set of genes, and every gene cannot be simply linked to a single outcome·
- Some genes are expressed only at certain times or under specific conditions.

Regulation of gene expression

- It includes various mechanisms used to increase or decrease the production of specific gene products (protein)
- The expression of a gene is a highly regulated process.
- Gene regulation involves a complex web of interactions that lead to the expression of some genes and the suppression of others, depending on circumstances.

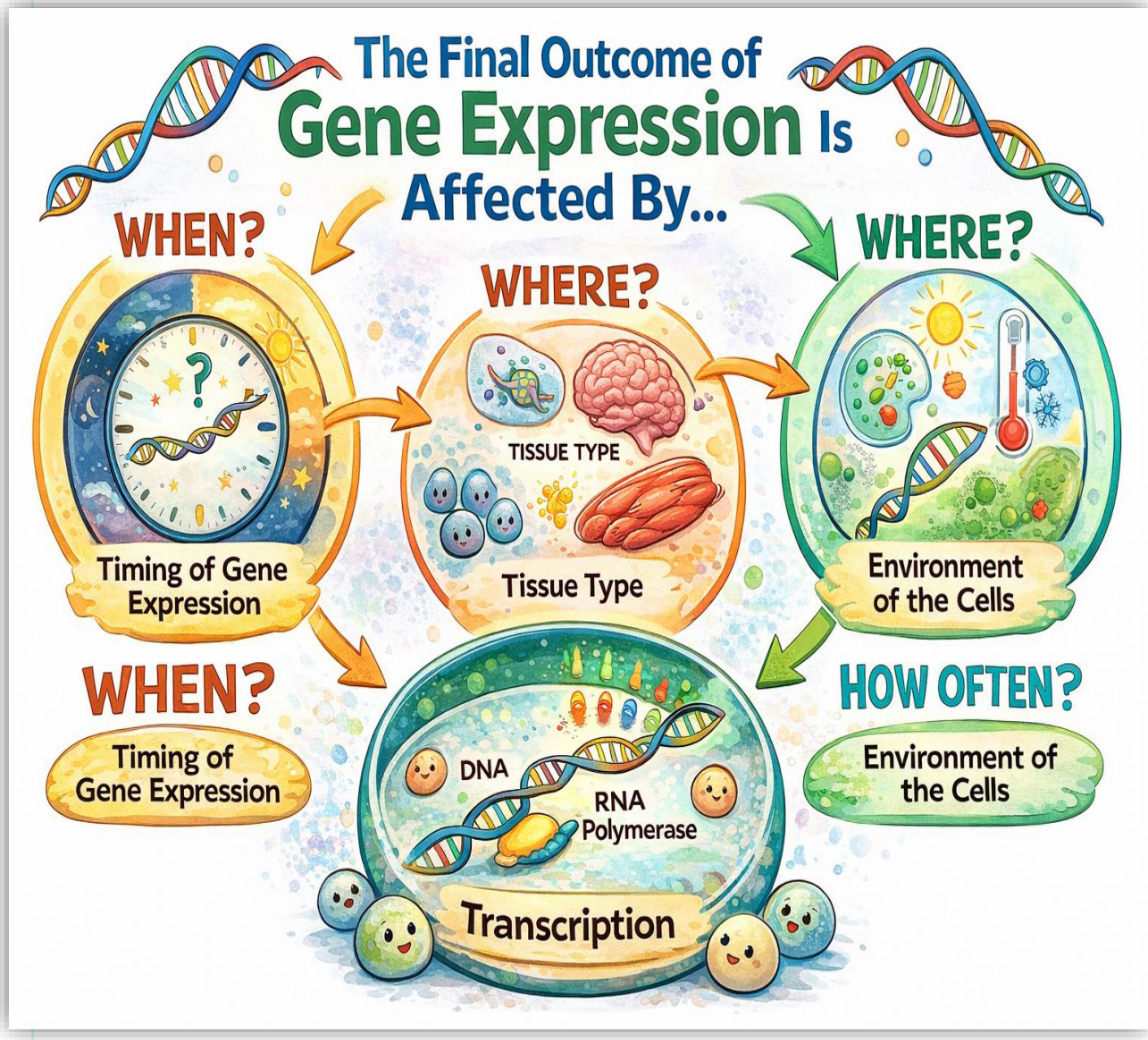


Regulation of gene expression

- **The final outcome of gene expression is affected by:**
  - The timing of gene expression

    "**When** a gene should be transcribed?
  - The tissue type "**Where**? In which tissue it should be transcribed?"
  - The environment of the cells

    "**How often** it should be transcribed?"

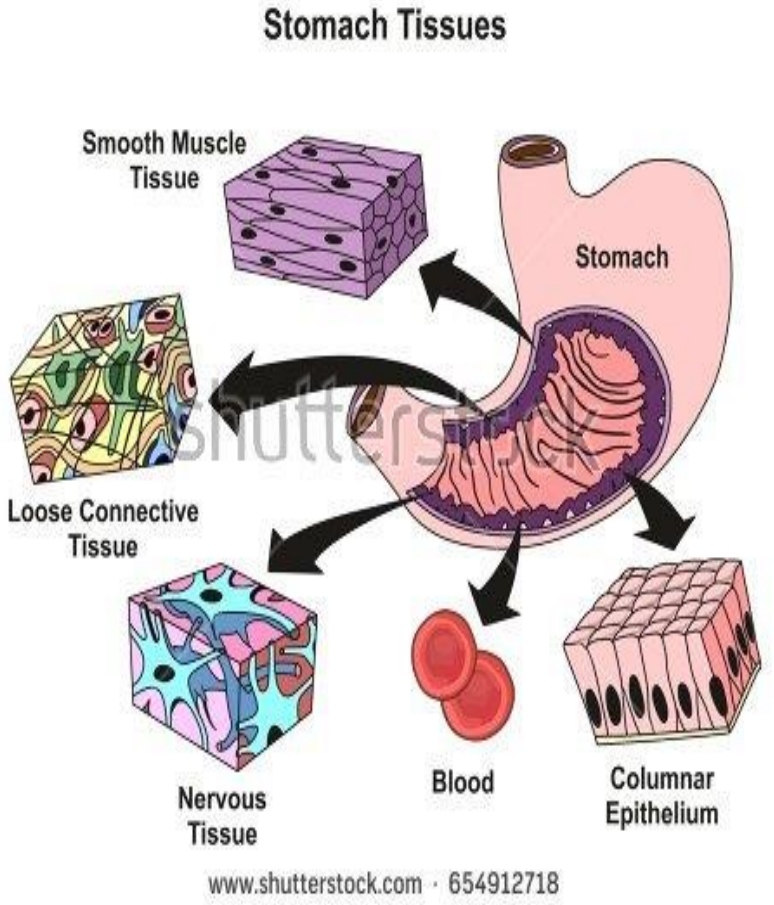


Importance of Regulation of gene expression

1- Tissue – specific expression : The genetic information in each somatic cell is the same

But

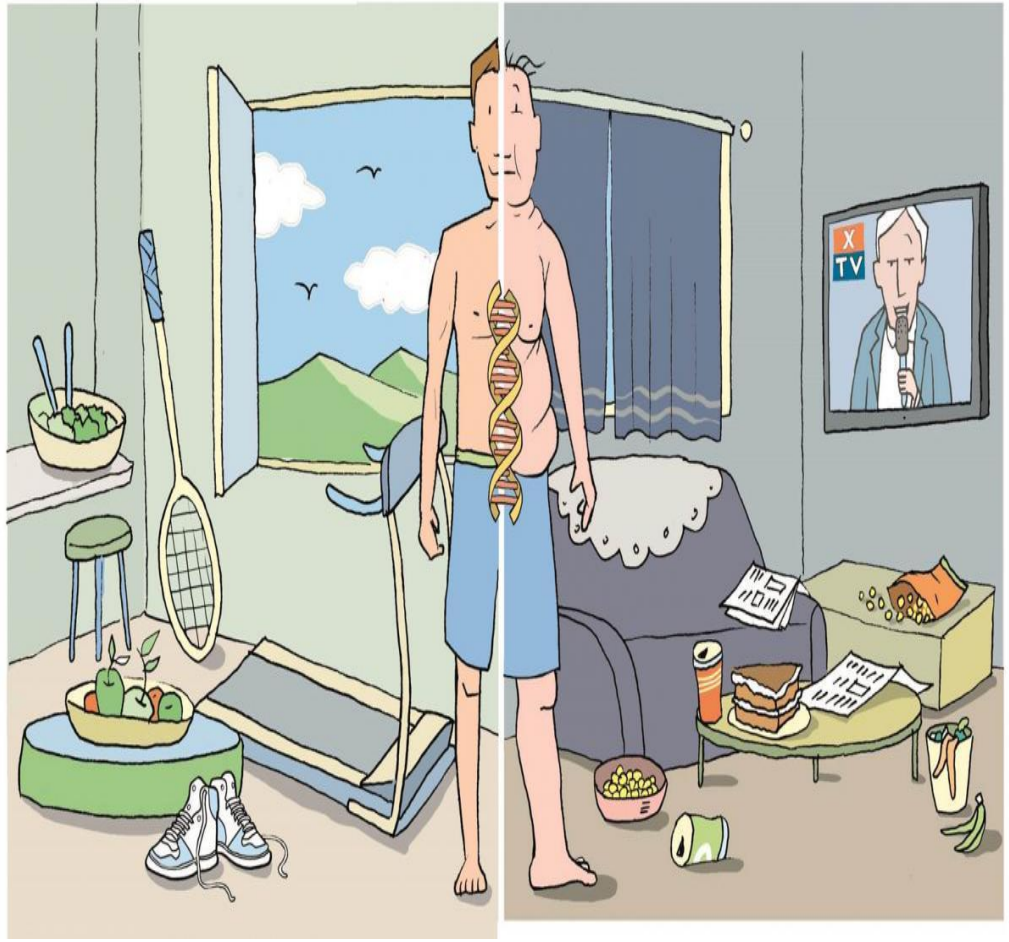
The difference between different tissues depend on the pattern of genes expression in these tissues .



Regulation of gene expression

2-The human cells **adapt to environmental changes** By altering gene expression.

3- Dysregulation of gene regulation can lead to **disease**



Types of Genes

1. Constitutive (Housekeeping) genes:

2. Regulated (Inducible &/or Repressible) genes:

- **Constitutive (Housekeeping) genes:**

  Genes that are almost always active (expressed at constant rate) in almost all cells, because they provide essential functions, such as energy production (glycolysis) or structural support (actin).

Types of Genes

2. Regulated (Inducible &/or Repressible) genes:

- ❑ Genes that expressed only at certain conditions & fluctuate **based on the cell's needs**
- ❑ Types:

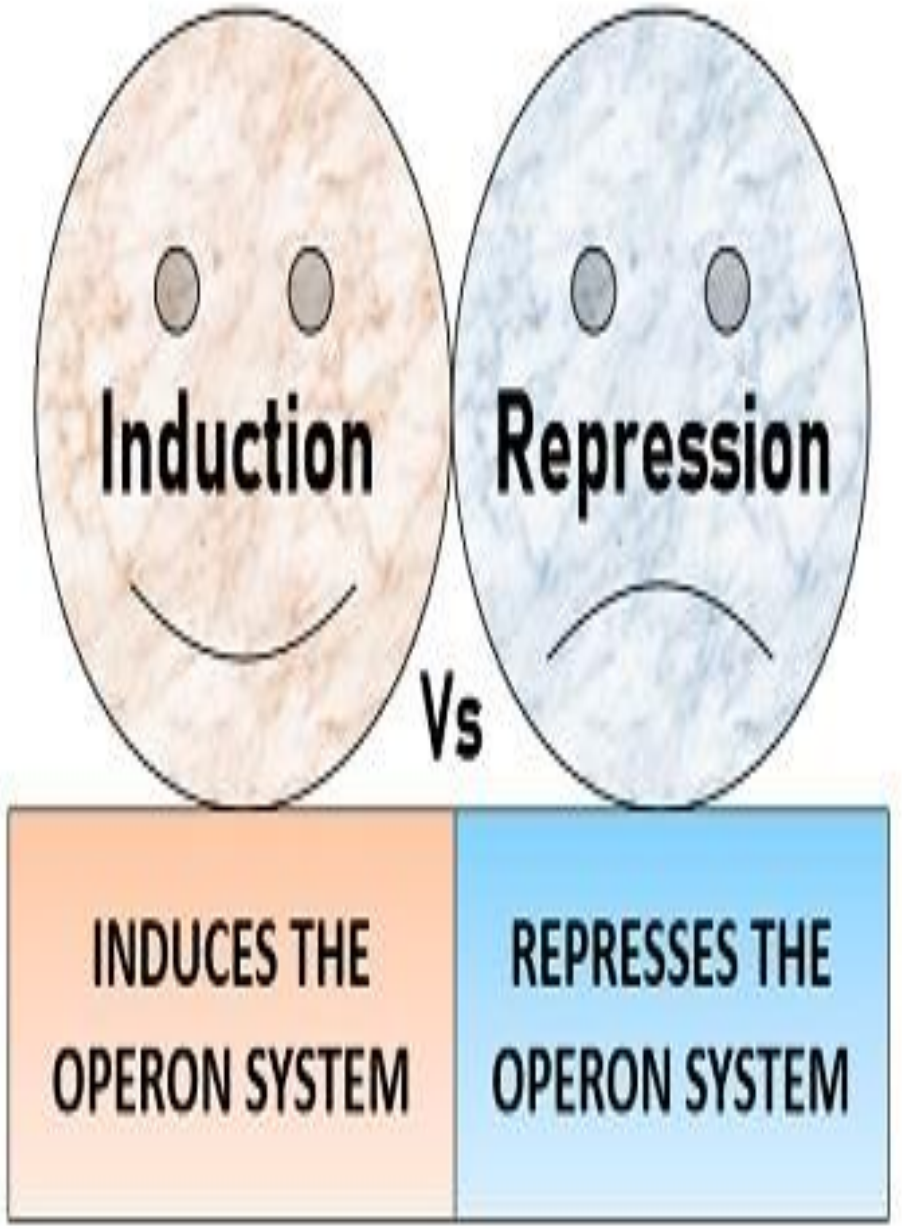
➢ **Inducible genes:**

Expression of inducible gene increased in response to inducer (when needed).

➢ **Repression:**

Expression of repressible gene decreased in response to repressor (when it is not required).

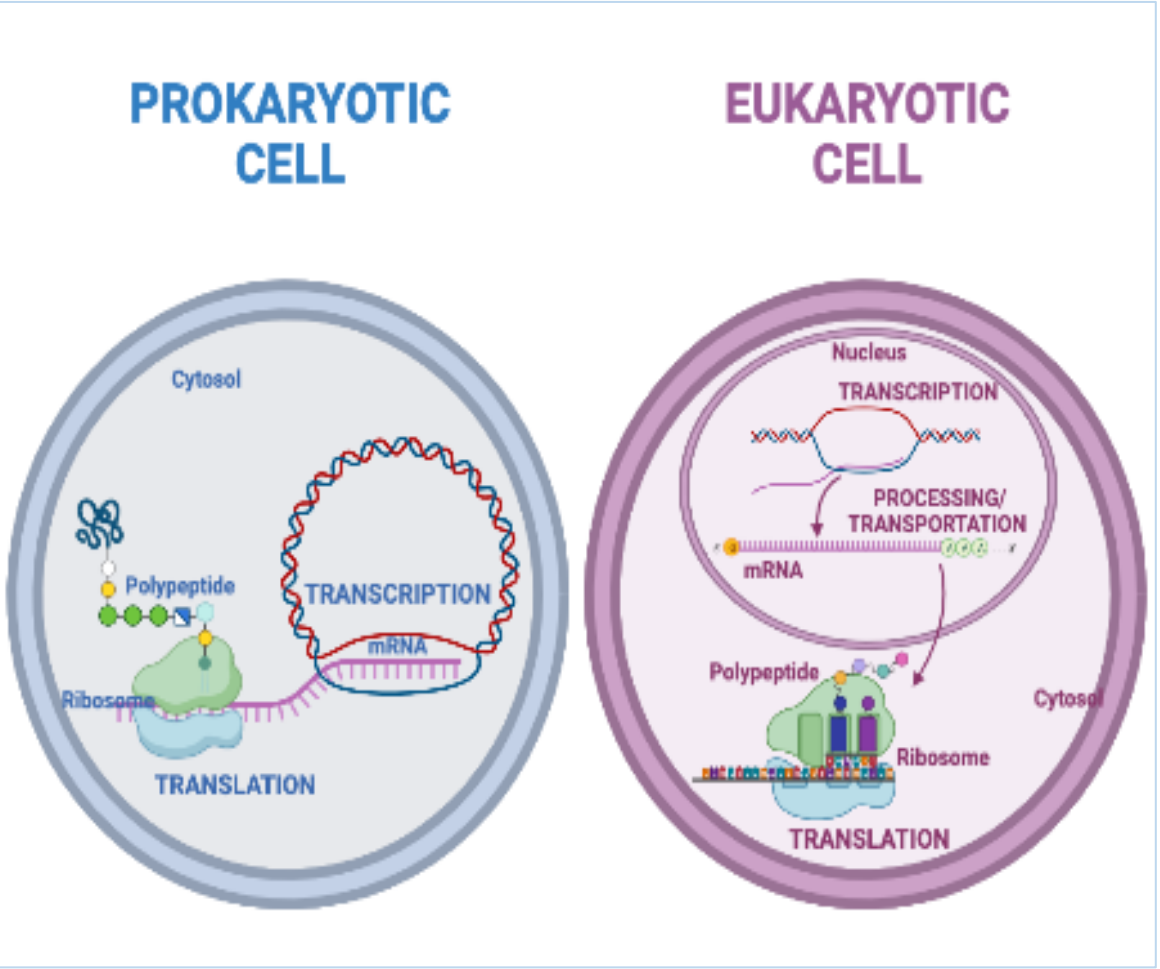
- ❑ E.g. Expression of insulin gene in pancreas.



Prokaryotes and eukaryotes gene expression

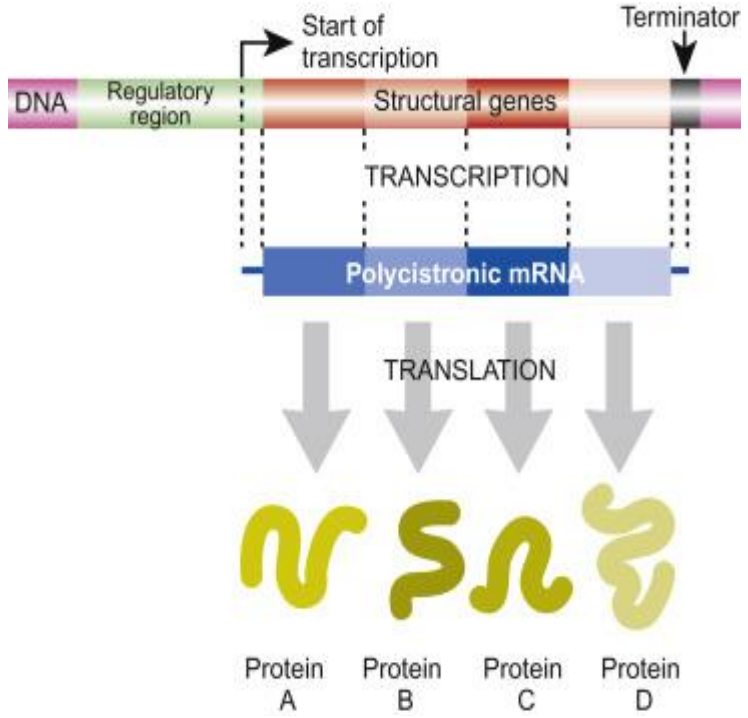
- Prokaryotes and eukaryotes share some similarities in their mechanisms to regulate gene expression; however, gene expression in eukaryotes is more complicated.

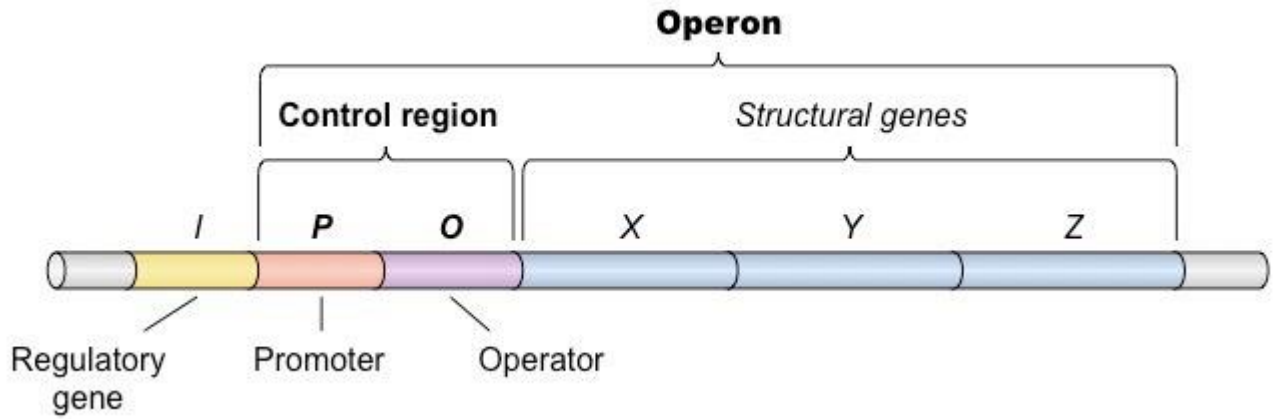
- Whereas regulating gene expression in multicellular organisms allows for cellular differentiation, in single-celled organisms like prokaryotes, it **primarily ensures that a cell's resources are not wasted in making proteins that the cell does not need at that time.**



Prokaryotic Gene Regulation

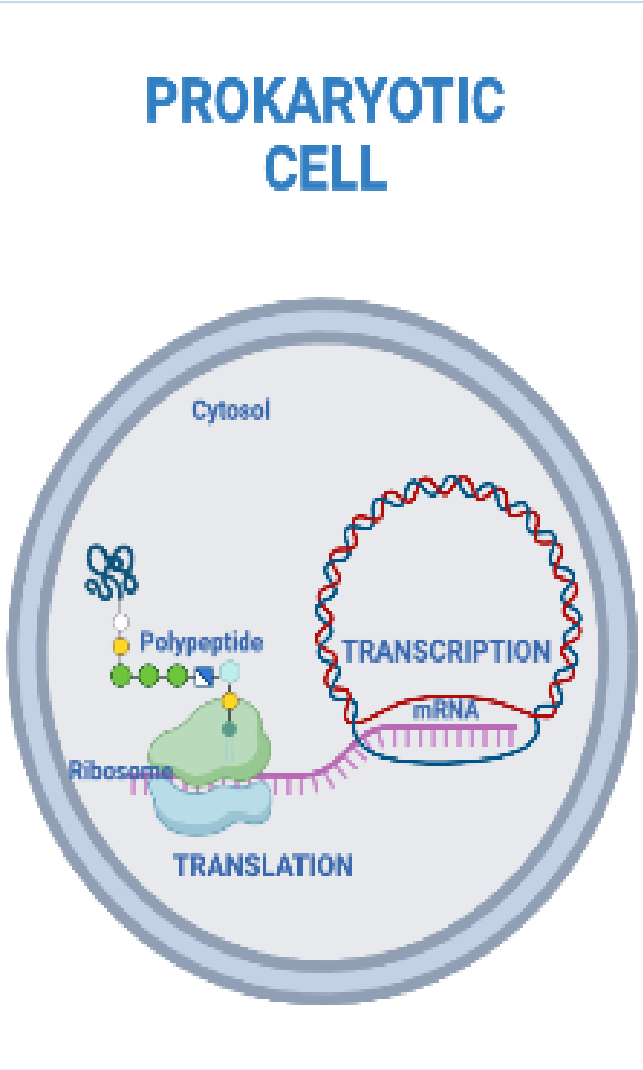
- In **Prokaryotic cells**, structural proteins with related functions are usually encoded together within the genome in a block called an **operon** and are transcribed together under the control of a single **promoter**, resulting in the formation of a polycistronic transcript.





Regulation in Prokaryotes (The Operon Model)

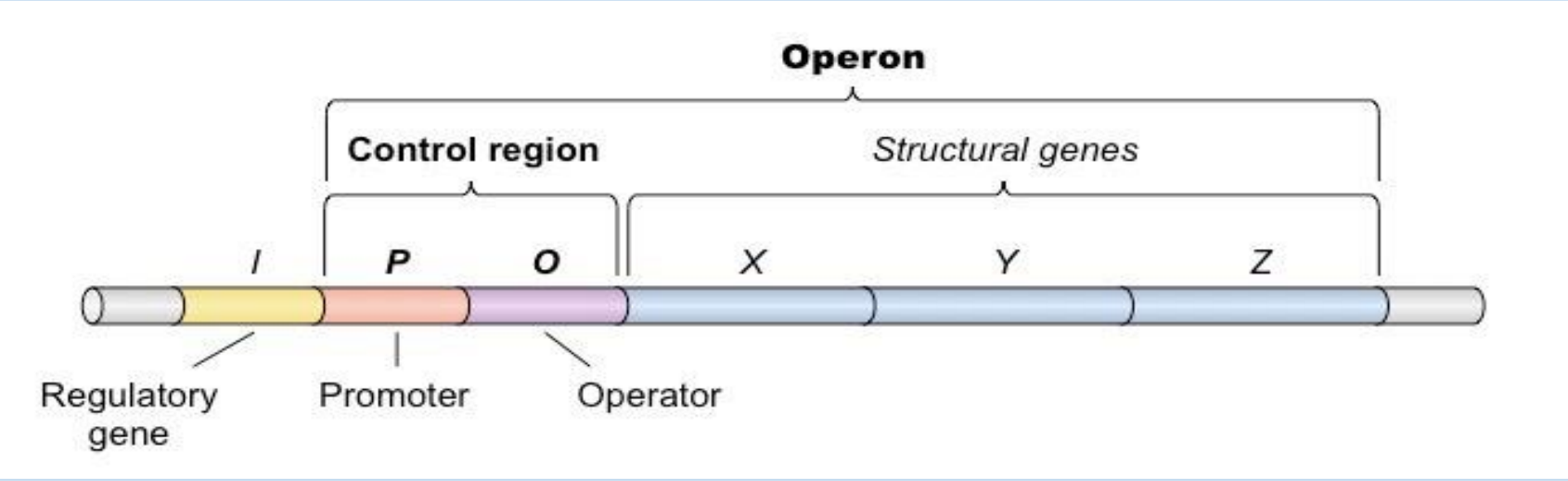
- **Simpler System:** Transcription and translation occur simultaneously in the cytoplasm since prokaryotes lack a nucleus.
- **Key Feature:** Regulation occurs primarily at the transcriptional level
- **The Operon:** A cluster of functionally related genes controlled by a single promoter



What is Operon

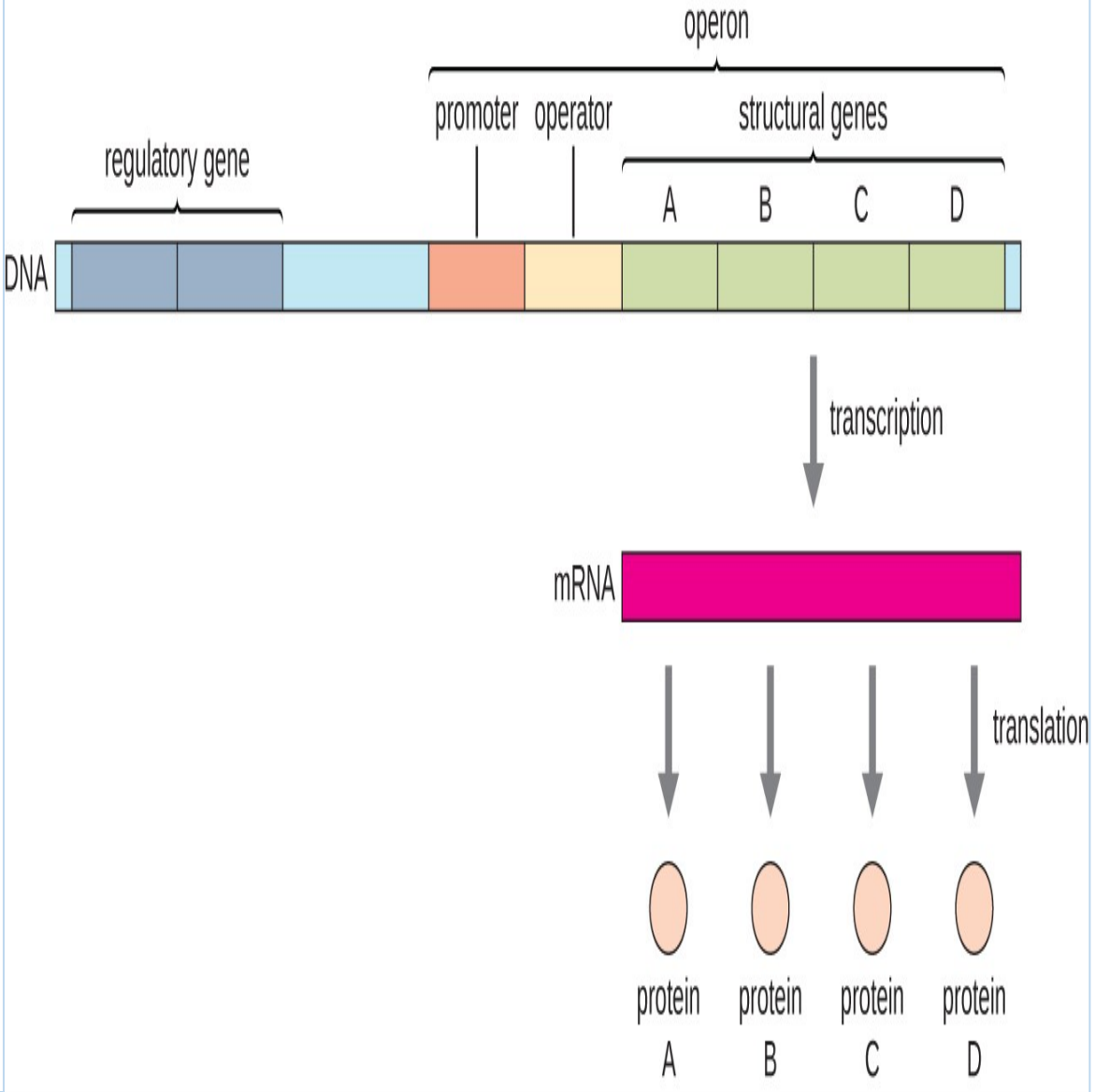
Operon is a segment of DNA strand consisting of:

- **1. Structural genes**, cluster of adjacent genes that carry the codons which can be translated into proteins (eg enzymes or structural proteins
- **2. Control (Regulatory) region**, which control the activity of structural genes and regulate gene expression



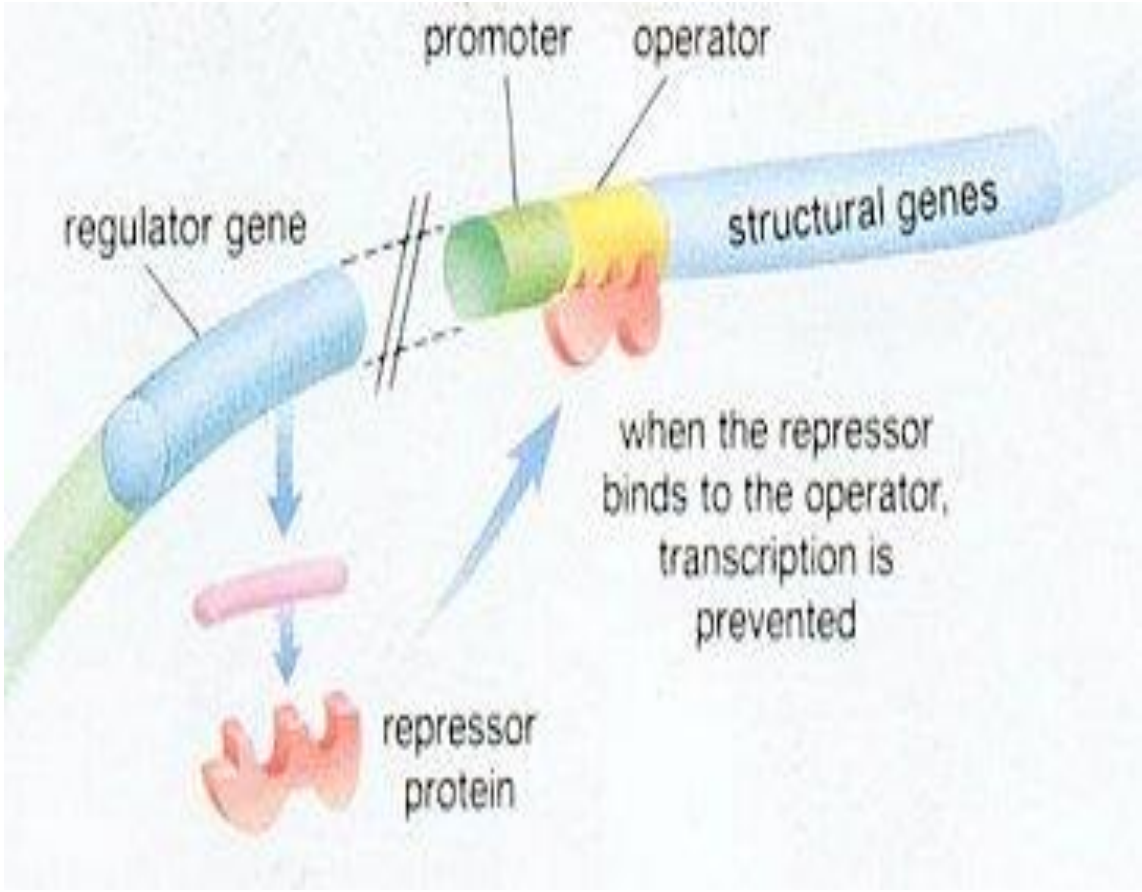
Operon: Regulatory region

- **Controller (Regulatory) region :** composed of
- **1. Promoter (P):** Part of DNA which control the activity of RNA polymerase and initiation of mRNA transcription.
- **2. Operator (O):** It is a part of operon DNA which control the activity of one or more structural genes, to which repressor protein is binded.
- =/-**3. Regulator (R):** These genes are responsible for production of specific protein called **repressor.** It binds with operator genes and turn off the synthesis of mRNA.



Gene Regulation in Prokaryotes: Inducible & Repressible Operons

- **Inducible and repressible operons** are two ways prokaryotic cells regulate gene expression.
- Prokaryotic operons are commonly controlled by binding of repressors to operator regions, which blocks the movement of RNA polymerase and prevent the transcription of operon structural genes by RNA polymerase. Thus, protein synthesis can be inhibited.

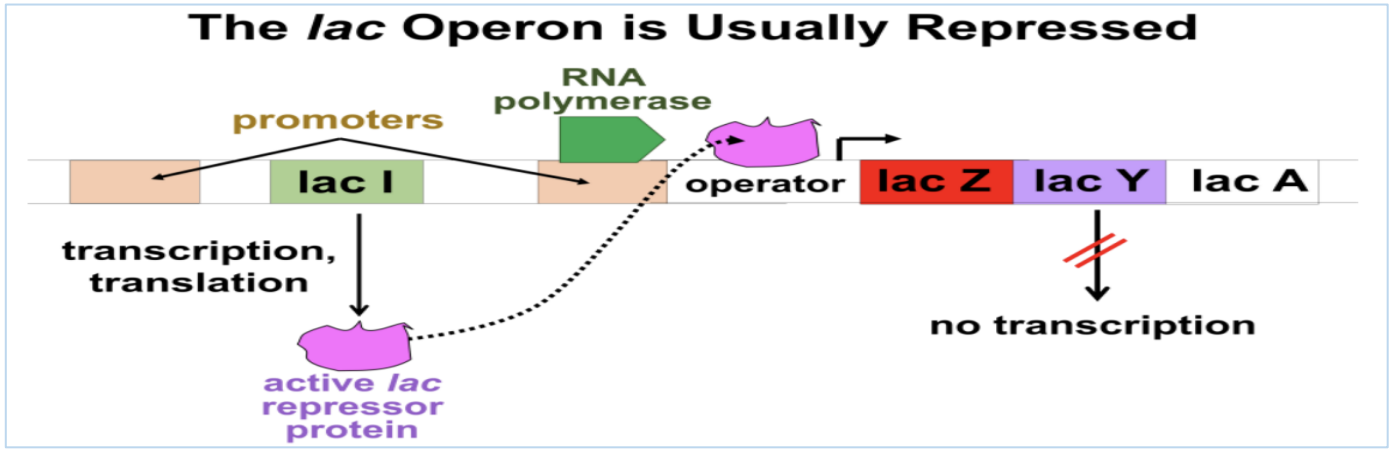


Gene Regulation in Prokaryotes: Inducible & Repressible Operons

- **An inducible operon is normally OFF.**
  - It is turned ON when a molecule called an inducer is present.
  - The inducer removes the block on transcription, allowing the genes to be expressed.
  - The inducer binds to and inactivates the repressor, allowing RNA polymerase to transcribe the genes.
- **A repressible operon is normally ON.**
  - It is turned OFF when a molecule called a corepressor is present.
  - The corepressor enables the repressor protein to block transcription.
  - The corepressor binds to and activates the repressor, which then binds the operator and blocks RNA polymerase.

Inducible Operon: The Lac Operon

- The lac operon is an example of an inducible operon regulated by lactose.
- The presence of lactose in a cell induces the transcription of the lac operon, which encoding enzymes in a pathway involved in the metabolism of lactose.
- These enzymes are required only when lactose is available.



The Lac Operon Structure

❑**Structural Genes:** (encode enzymes needed to degrade lactose in *E. coli*)

- lacZ: Encodes beta-galactosidase, which breaks lactose into glucose and galactose
- lacY: Encodes permease, which helps lactose enter the cell
- lacA: Encodes transacetylase enzyme

❑**Regulatory Elements:**

- Promoter (P): Binding site for RNA polymerase
- Operator (O): Binding site for the repressor
- Lac I: A separate gene that produces the repressor protein

Lac Operon Mechanism

- **Preference**: Bacteria prefer glucose over lactose

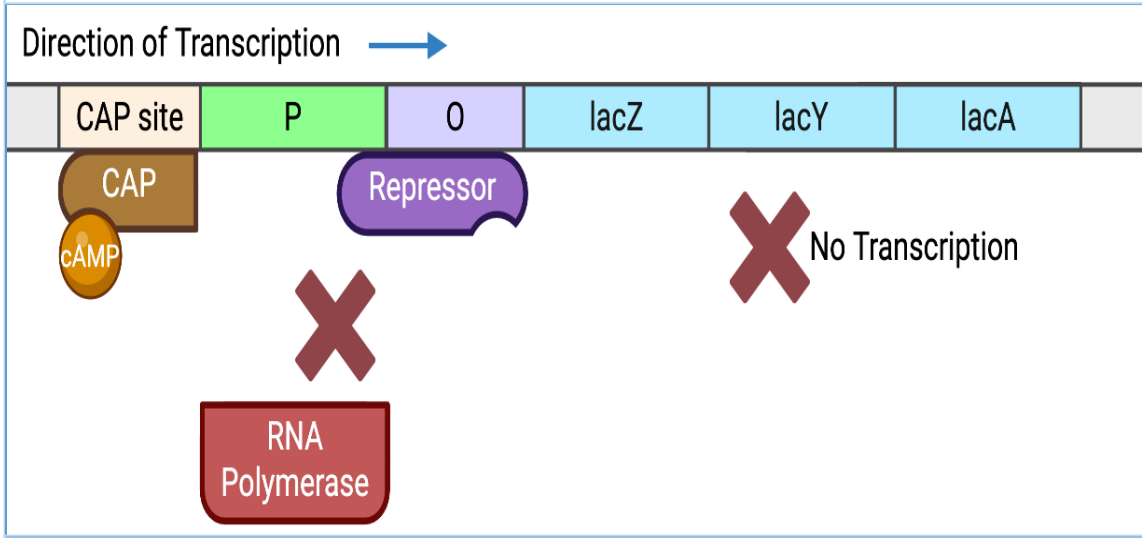
- **In the Absence of Lactose (& low glucose)**

The repressor binds to **the operator**, blocking RNA polymerase and stopping transcription

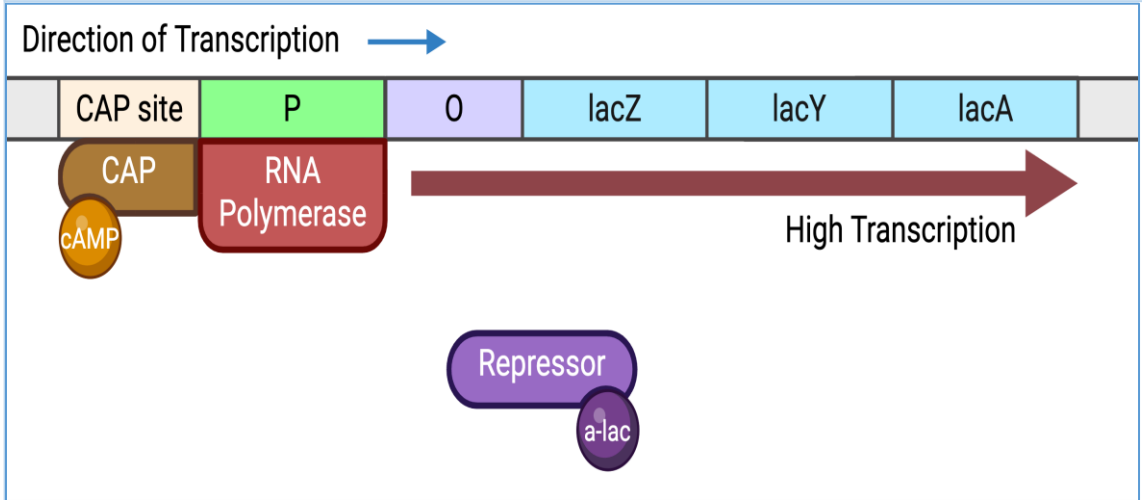
- **In the Presence of Lactose (& low glucose):**

Lactose is converted to **allolactose** (the inducer), which binds to the repressor, causing it to release from the operator & allowing transcription to proceed

Low Glucose & Low Lactose



Low Glucose & High Lactose



Glucose Control (Catabolite Repression) in lactose presence

❑When glucose is low:

- This activate adenyl cyclase which synthesize cAMP from ATP. cAMP levels then rise and bind to the **Catabolite Activator Protein (CAP)** forming the CAP-cAMP complex.

- The **CAP-cAMP complex** binds to, a **CAP binding site** is located upstream of the promoter, in the regulatory regions of these operons.

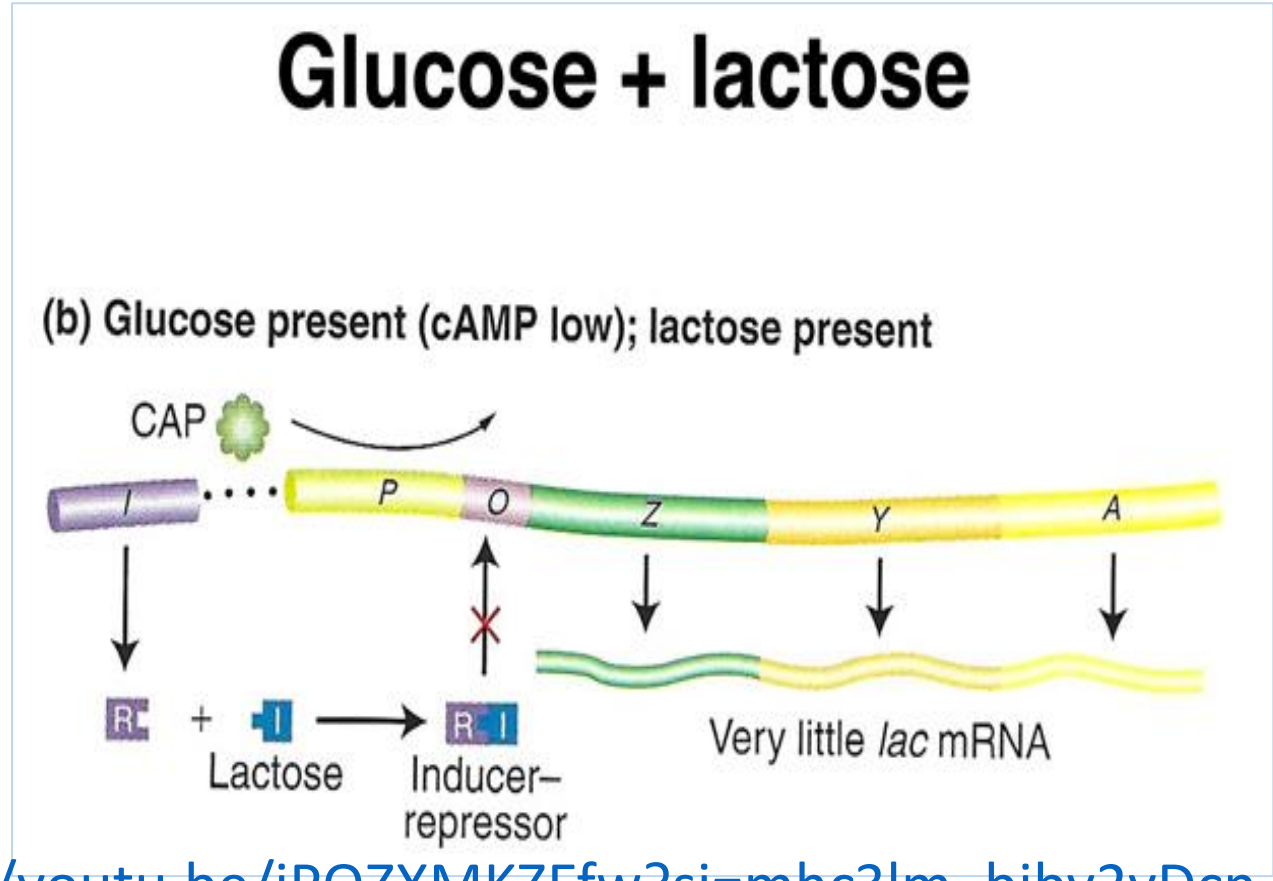
- Binding of the CAP-cAMP complex to this site increases the binding ability of RNA polymerase to the promoter region to initiate the transcription of the structural genes, ensuring the lac operon is only highly active when glucose is absent

Glucose Control (Catabolite Repression) in lactose presence

❑ When glucose levels are high:

- Because of low cAMP levels under these conditions, there is an insufficient amount of the CAP-cAMP complex to activate transcription of these operons.

- There is **catabolite repression** of operons encoding enzymes for the metabolism of lactose



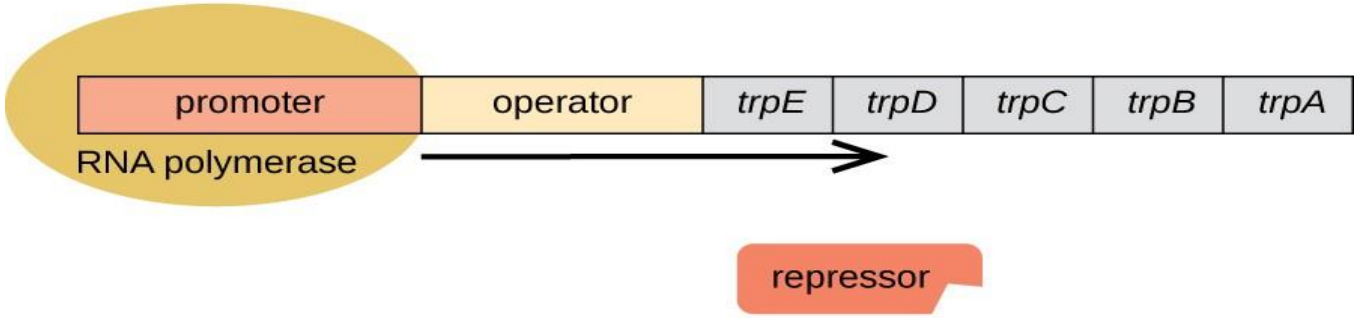
- https://youtu.be/iPQZXMKZEfw?si=mhc3lm_bjby2vDcn

❑ Thus, for the lac operon to be expressed, there must be **activation by cAMP-CAP as well as removal of the lac repressor from the operator**.

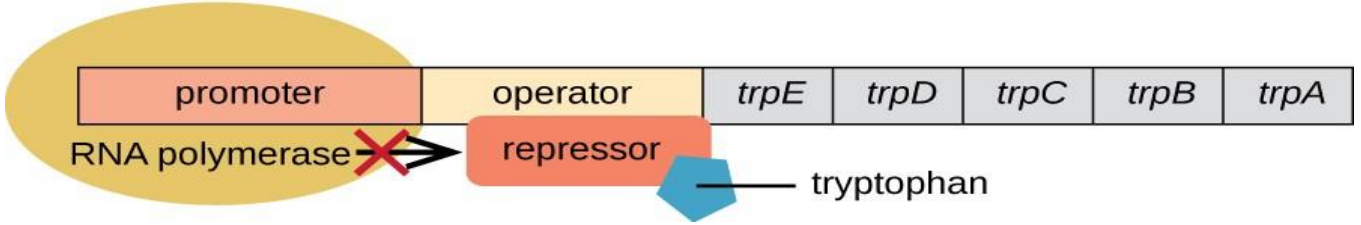
A repressible operon : Tryptophan Operon

- A repressible operon is normally ON.
  - It is turned OFF when a molecule called a corepressor is present.
  - The corepressor (Tryptophan) binds to and activates the repressor, which then binds the operator and blocks RNA polymerase and inhibit transcription

In the absence of tryptophan, the *trp* repressor dissociates from the operator, and RNA synthesis proceeds.



When tryptophan is present, the *trp* repressor binds the operator, and RNA synthesis is blocked.



Five structural genes needed to synthesize tryptophan in E. coli are located next to each other in the trp operon.

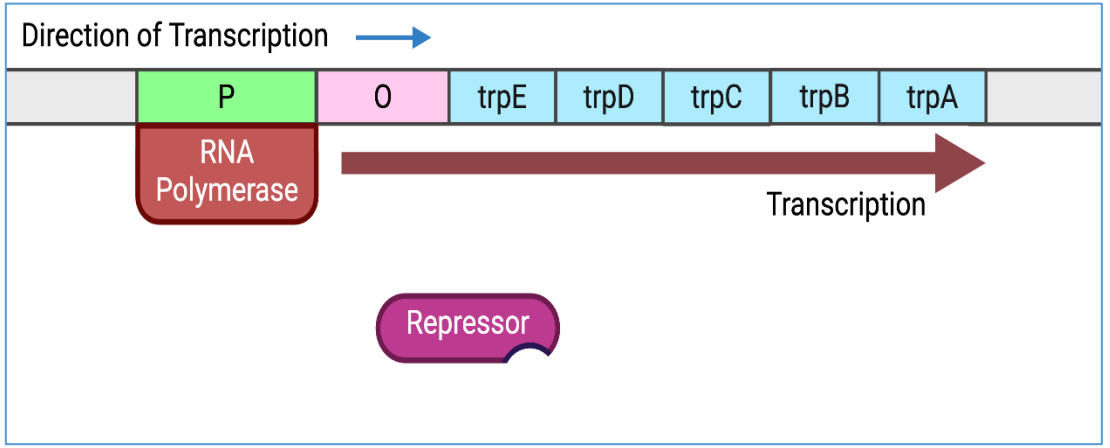
A repressible operon : Tryptophan Operon

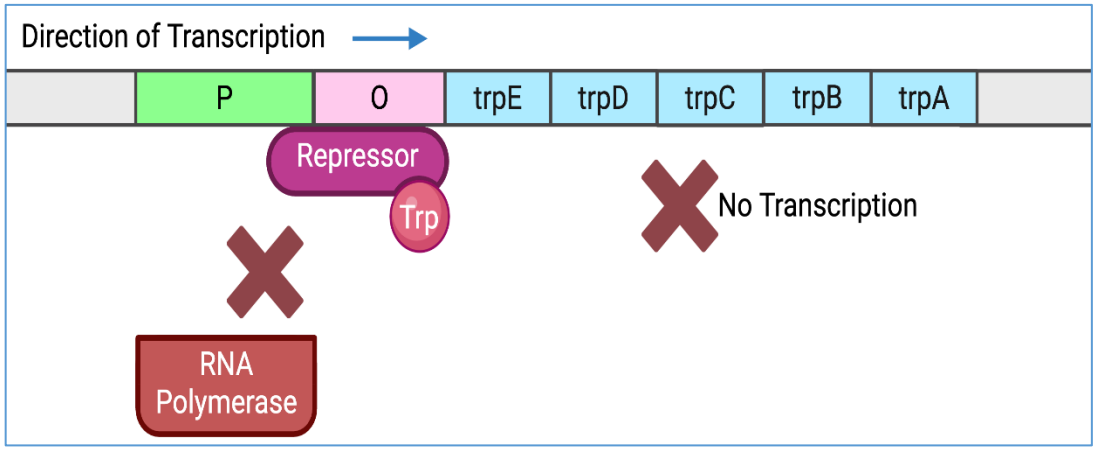
❑ When Tryptophan is absent in the cell:

- The cell transcribes the trp genes that allow the cell to produce tryptophan.

❑ When Tryptophan is present :

- The cell does not need to produce tryptophan. In this situation, transcription of the trp operon is prevented when tryptophan binds the repressor protein, causing the repressor protein to bind DNA at the operator region and block transcription.





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Lac Operon vs. Trp Operon

Inducible System

Lac Operon

Works With Lactose

+ Lactose Binds → Genes ON

Lactose Present

Genes Turned ON

Repressible System

Trp Operon

Works With Tryptophan

+ Tryptophan Binds → Genes OFF

Tryptophan Present

Genes Turned OFF

Prokaryotes and eukaryotes gene expression

- While regulation of Prokaryotes gene expression occurs only at the level of transcription, eukaryotes gene expression **regulation occurs at several levels:**

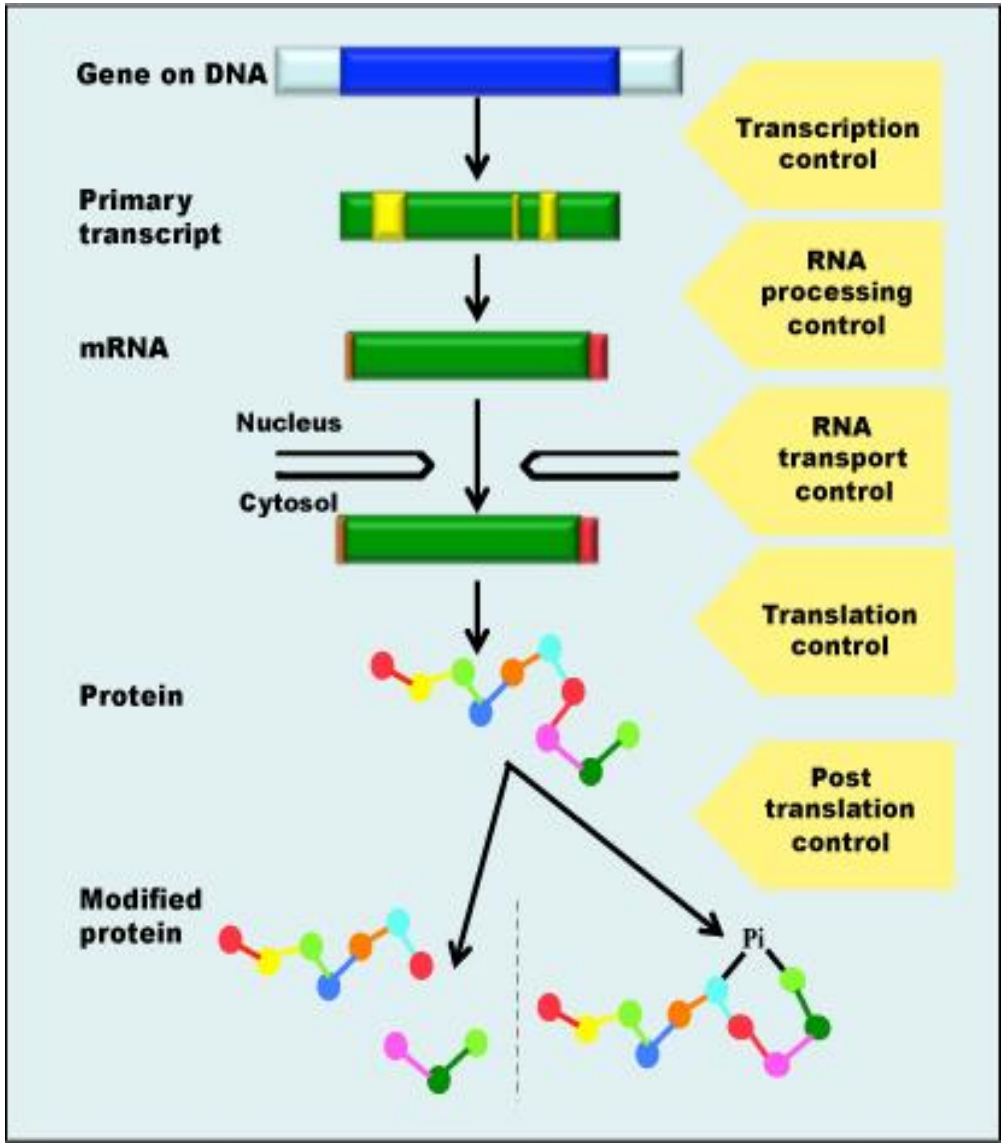
  A. **Control at DNA level**

  B. **Control at transcription level**

  C. **Control at post-transcriptional level**

  D. **Control at translational level**

  E. **Control at post-translational level**



Assignment. Answer the following questions

- **What is the default mode of the lac operon when allolactose is absent?**
- **Does allolactose act as an inducer or a corepressor on the lac operon?**
- **The DNA sequence, to which repressors may bind, that lies between the promoter and the first structural gene is called the _____.**
- **What affects the binding of the *trp* operon repressor to the operator?**
- **How and when is the behavior of the *lac* repressor protein altered?**

best wishes