REULATION OF GENE EXPRESSION

- *Living cells adapt to changes in environment by regulating gene expression*
- *Eg: insulin is synthesized only by specialized cells of Pancreas*
- *Regulatory mechanisms allows expression of insulin genes only in pancreas, while preventing its expression in other cells*

Types of regulation

- ***Positive regulation*** –
  - *When expression of genetic information is quantitatively increased by the presence of a regulating element [activator/inducer]*
- ***Negative regulation*** –
  - *When expression of genetic information is quantitatively diminished by the presence of a regulating element [repressor]*

Types of genes

- ***Inducible genes*** –
  - *expressed only when a specific regulatory substance inducer/activator is present.*
  - *Eg: glucokinase induced by insulin in human*
- ***Constitutive genes*** –
  - *Expression is not regulated*
  - *Expressed at a constant rate as the proteins are required all the time in the cell [house keeping gene]*
  - *Eg: enzymes of TCA cycle*

Regulation in prokaryotes

- *Have a simple mechanism for regulation of genes*
- *prokaryotes adapt by turning groups of genes 'on' and 'off' in response to various environmental signals*
- *Genes involved in a particular metabolic pathway are often arranged in a linear fashion called 'operon'*

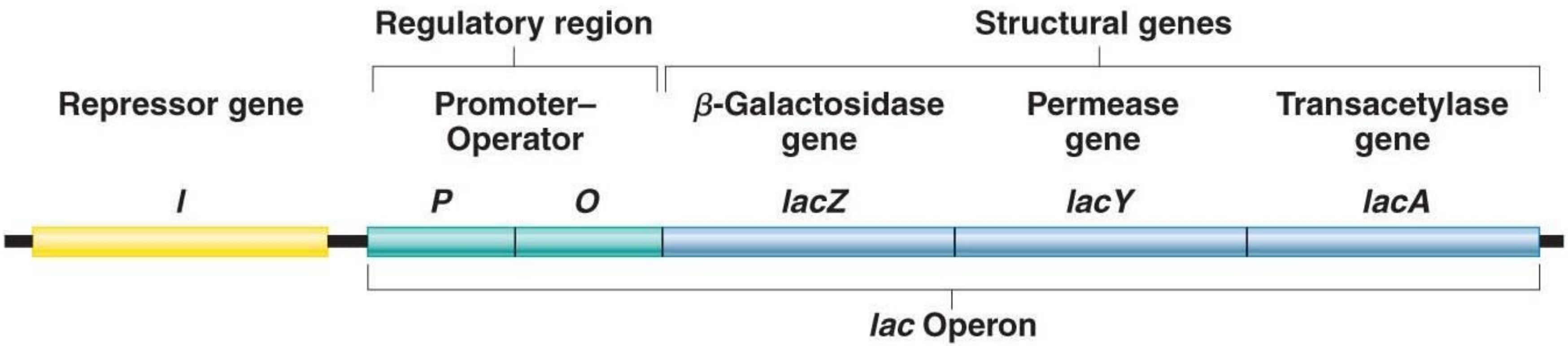
- *An operon is a cluster of bacterial genes along with an adjacent promoter that controls the transcription of those genes*
- *Eg: lactose operon [lac operon] for regulation of lactose metabolism*
- *Galactose operon [gal operon] for regulation of galactose metabolism*

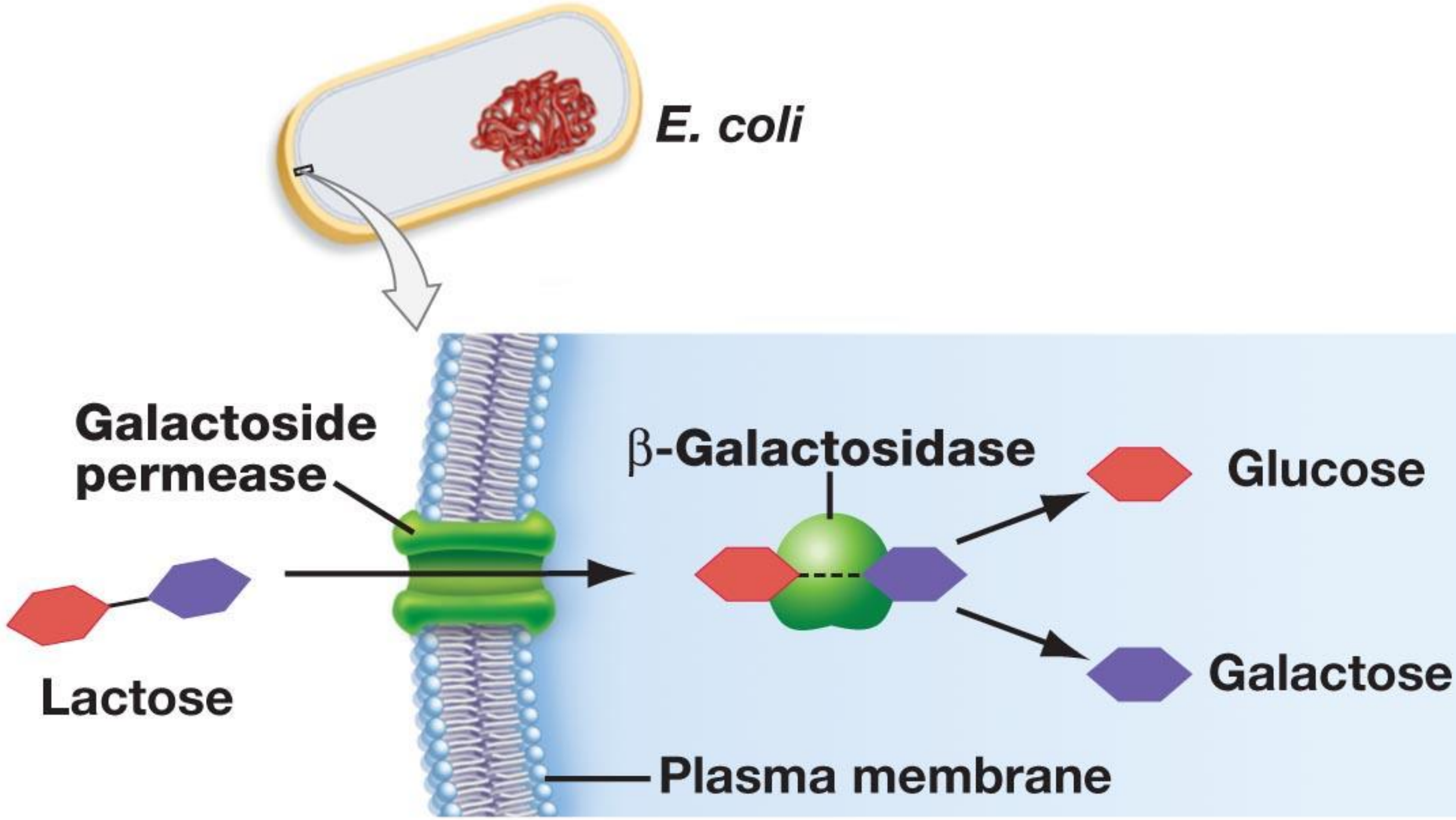
Lac operon

- *Jacob and Monod in 1961 [Nobel prize in 1965] described lac operon in e.coli*
- *A unit of gene expression to make the enzymes necessary to metabolize lactose*
- *Glucose is the preferred and most frequently available energy source for E. coli. The enzymes to metabolize glucose are made constantly*

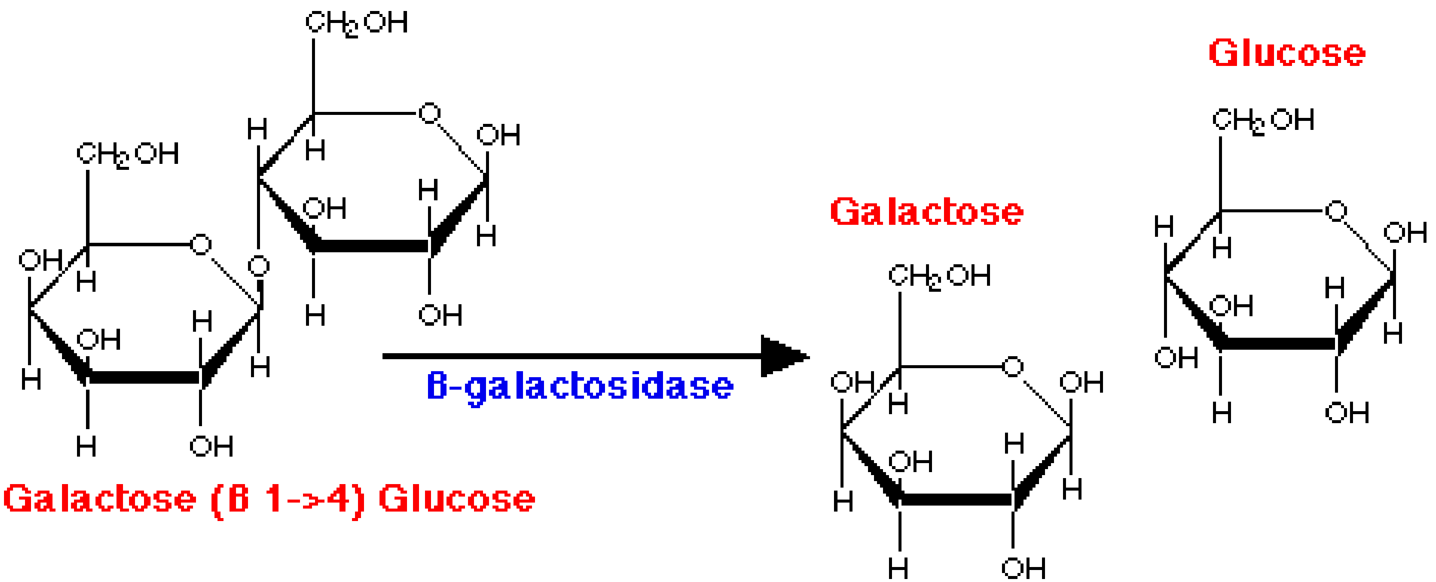
- *Whenever glucose is present, E.coli metabolizes it before using any alternative energy sources such as lactose, arabinose, galactose, and maltose*
- *When both glucose and lactose are available, the genes for lactose metabolism are transcribed at very low levels.*
- *Only when the supply of glucose has been exhausted, RNA polymerase start to transcribe the lac genes efficiently, which allows E.coli to metabolize lactose*

- *Lac operon contain the following elements*
  - *Repressor/inhibitor gene [lac i] – produces repressor protein*
  - *Promoter site [P] – containing cap binding site and RNAP binding site*
  - *Operator site [O] – repressor protein binds and blocks initiation*
  - *Structural genes [lac Z, lac Y, lac A] – code for β-galactosidase, galactoside permease and thiogalactoside transacetylase respectively, required for lactose metabolism*


Regulatory region
Structural genes
Repressor gene
Promoter–Operator
β-Galactosidase gene
Permease gene
Transacetylase gene
I
P
O
lacZ
lacY
lacA
lac Operon


E. coli
Galactoside
permease
β-Galactosidase
Glucose
Lactose
Galactose
Plasma membrane

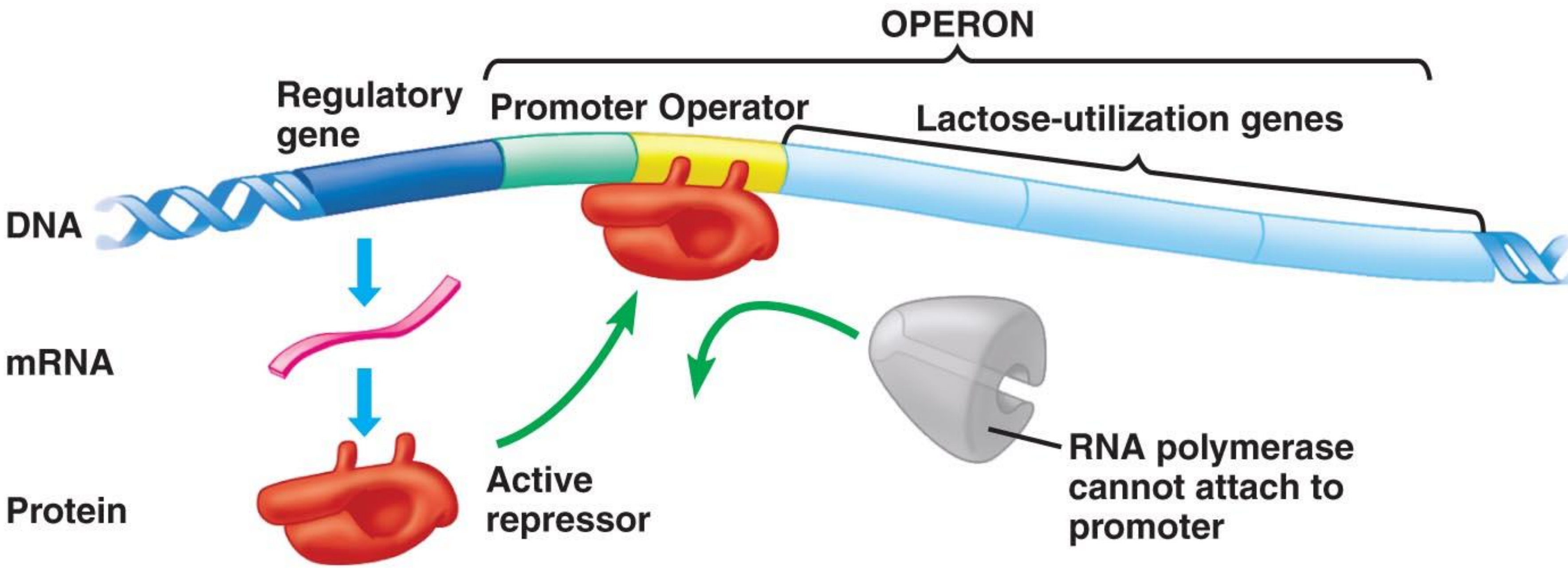
Lactose



Galactose (β 1->4) Glucose

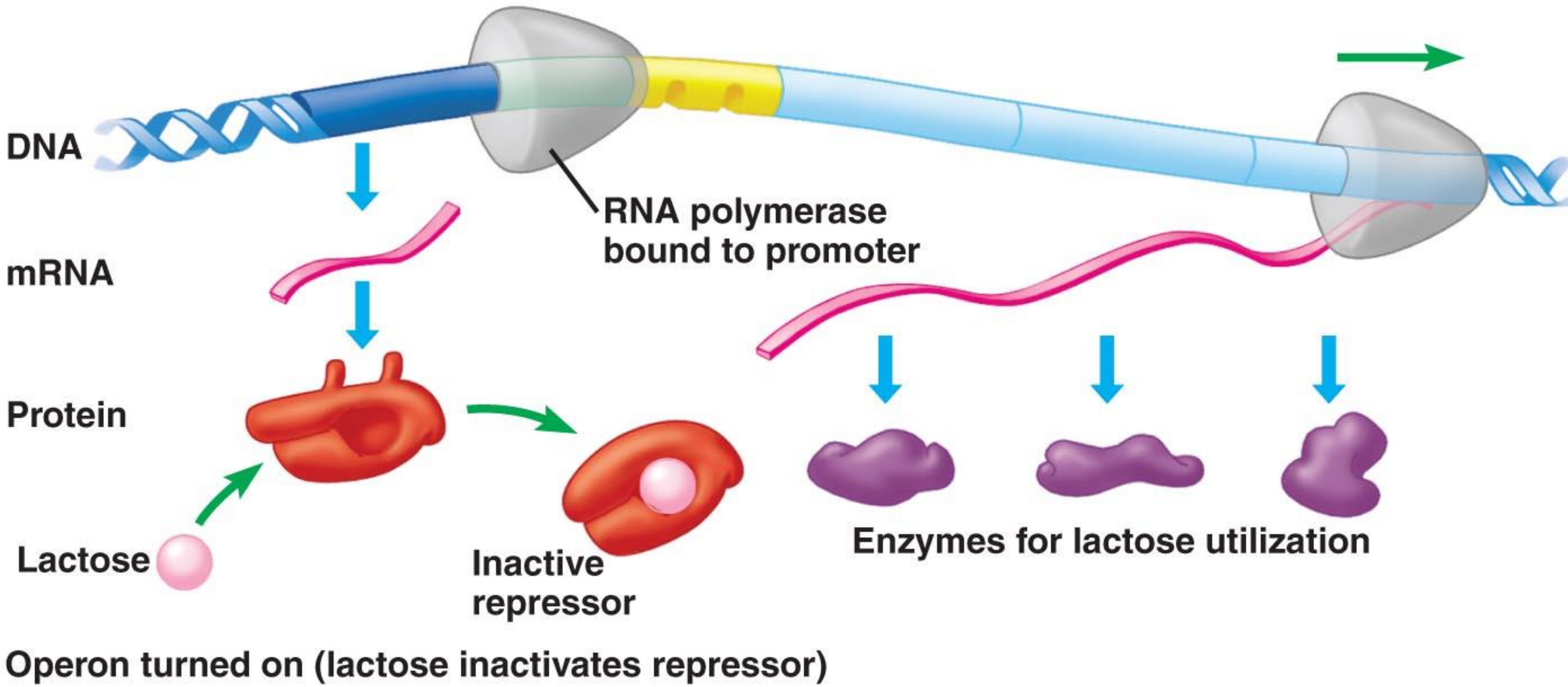
- *Thiogalactoside transacetylase [Galactoside O-acetyl transferase]*
- *acetyl-CoA + beta-D-galactoside → CoA + 6-acetyl-beta-D-galactoside*

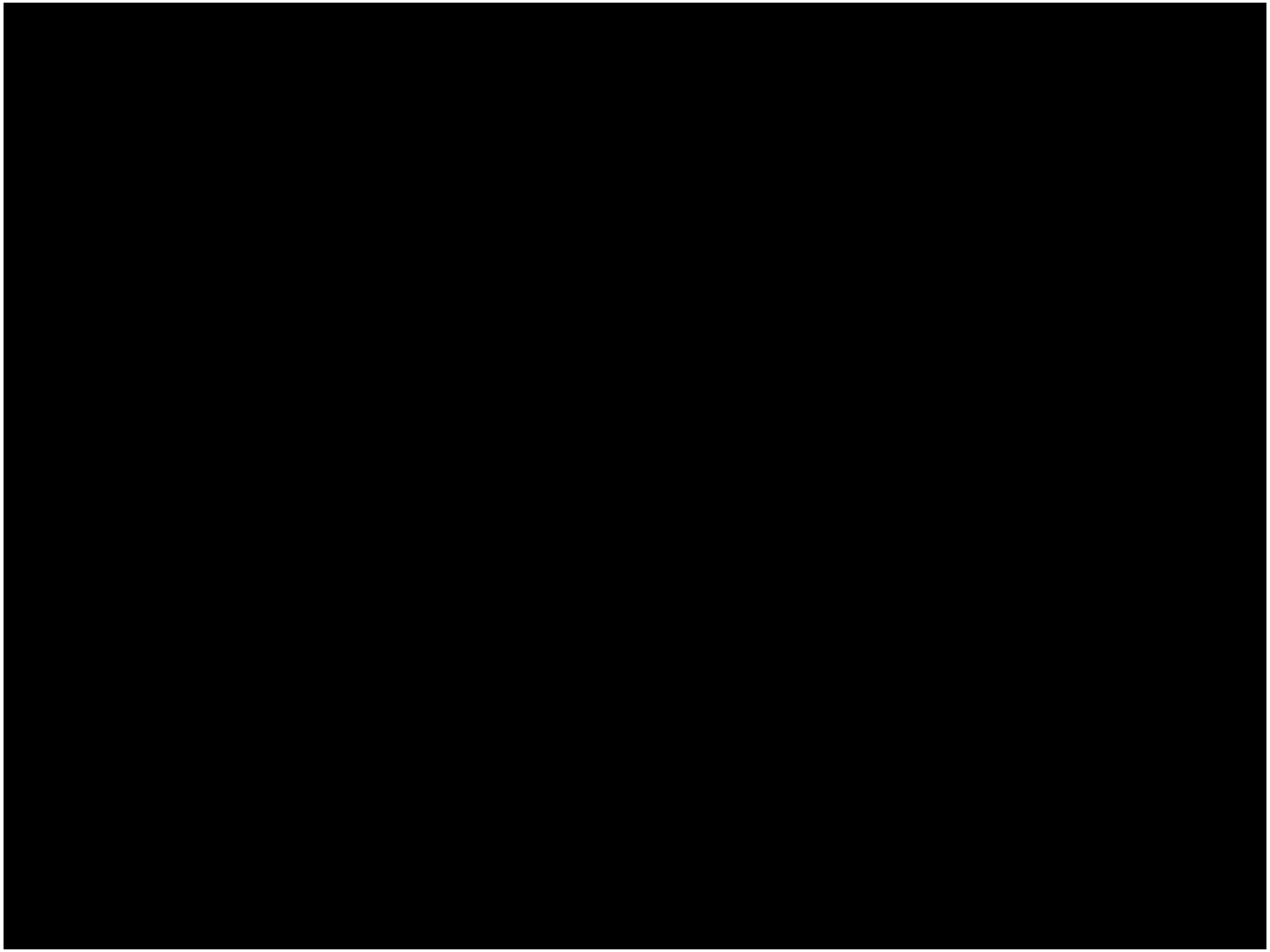
- ***Repression of lac operon [in the absence of lactose]****–*
  - *Lac I is a constitutive gene [expressed at a constant rate] which produce lac repressor*
  - *Repressor specifically bind lac O*
  - *Prevent binding of RNAP to promoter site*
  - *Blocking transcription of Z, Y, A*
  - *Repressor act as negative regulator of gene expression*



Operon turned off (lactose absent)

- ***De-repression of lac operon [in the presence of lactose]*** *–*
  - *Repressor molecule have high affinity for lactose*
  - *Bind to and induce conformational change in the repressor*
  - *Repressor get inactivated and cannot bind to lac O*
  - *Transcription proceeds expressing 3 enzymes*
  - *Lactose induces the synthesis of these 3 gens*
  - *Act by inactivating the repressor molecule*


DNA
mRNA
Protein
Lactose
RNA polymerase
bound to promoter
Inactive
repressor
Enzymes for lactose utilization
Operon turned on (lactose inactivates repressor)



Regulation in eukaryotes

- *Expression and regulation are more complex because –*
  - *Each cell contain the entire genome*
  - *Larger and complex genome*
  - *Different cell types*
  - *Genes not organized into operons, instead, spread widely across the genome*
  - *Transcription and translation are uncoupled*

Regulated by a variety of mechanisms –

1. *DNA level regulation*
2. *Transcriptional regulation*
3. *Post transcriptional regulation*
4. *Translational regulation*
5. *Post translational regulation*

1. DNA level regulation

- ***Gene amplification –***
  - *To produce large number of specific proteins, number of a gene is increased several fold*
  - *Commonly observed during developmental stages*
  - *eg: Drosophila [fruit fly] chorion [egg shell] gene amplified to make large quantities of proteins to surround egg during oogenesis*
  - *In other cells only 1 copy of the gene present*

- ***<u>Gene rearrangement –</u>***
  - *Segment of DNA is moved from 1 location to another in a genome*
  - *Produce different proteins*
  - *Eg: in B cells, producing antibodies, heavy chain gene of IgG is generated by rearranging the sequence large precursor into a single exon*

- ***<u>Gene loss –</u>***
  - *If chains are deleted or partially deleted, functional proteins cannot be formed*
  - *Eg: immature erythroblast contain nuclei with genes that code for globin chain of hemoglobin. As cells mature, nuclei extrude and no genome to produce globin*

- ***<u>Chemical modification –</u>***
  - *Cytosine on both DNA strands undergo methylation by methylase to form 5-ethyl cytosine*
  - *Resulting DNA remain inactive during differentiation*
  - *Important in preventing transcription of genes intended to be permanently turned off*

2. Transcriptional regulation

- ***Chromosomal packaging –***
  - *Regulates large area of chromosome containing many gene*
  - *Tight packing causes genes made inaccessible to form inactive heterochromatin*
  - *Eg: one X chromosome is inactivated in females by tight wounding*

- ***Individual gene regulation –***
  - *Transcription factors are necessary to attach and activate a gene*
  - *Function by binding to promoter or enhancer*

3. Post transcriptional regulation

- ***Alternative splicing –***
  - *Some genes produce related, but different proteins by alternative splicing*
  - *Calcitonin gene in thyroid gland produce calcitonin [in calcium regulation]*
  - *In neurons produce calcitonin related peptide [involved in taste sensation]*
  - *Difference in third coding exon position*

- ***Regulation of RNA stability –***
  - *hnRNA which are never processed to mRNA are degraded in nucleus*
  - *Some genes that code for long acting peptides [eg: β-globulin] have long half life [>10 hrs]*
  - *Some genes that code for short acting peptides [eg: growth factors] have short half life [<1 hr]*
  - *Longer poly A tail increase half life*

4. Translational regulation

- *Mostly affect initiation*
- *eIF_2 is inactivated by phosphorylation by protein kinase*
- *Heme inhibits protein kinase and enhance eIF_2 activity*

5. Post translational regulation

- ***Protein activation –***
  - *Some proteins are not active when formed*
  - *Eg: bovine pro insulin [inactive], cleaved into 2 peptides, 30 amino acids removed to form insulin [active]*

- ***<u>Feed back control –</u>***
  - *Product of a pathway inhibit the same pathway*
- ***<u>Protein degradation/ turnover –</u>***
  - *Proteins are constantly degraded to prevent formation of unwanted or abnormal proteins*
  - *Ubiquitin is a tag that labels proteins for degradation*
  - *It directs proteins to compartments in the cell which destroys and recycles proteins.*
  - *This discovery won the Nobel Prize for chemistry in 2004*

THANK YOU