AL-FARABI KAZAKH NATIONAL UNIVERSITY
FACULTY OF BIOLOGY AND BIOTECHNOLOGY
DEPARTMENT OF BIOTECHNOLOGY

Lecture 10

Regulation of Gene Expression

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Lecture Plan

1.Introduction: Why Regulate Gene Expression?
2. Levels of Gene Expression Regulation
3. Regulation in Prokaryotes: The Operon Model
4. The lac Operon: Negative and Positive Control
5. The trp Operon: Repression and Attenuation
6. Regulation in Eukaryotes: An Overview
7. Chromatin Remodeling and Epigenetic Regulation
8. Transcriptional Regulation: Transcription Factors and Enhancers
9. Post-Transcriptional Regulation: RNA Processing and Stability
10. Translational and Post-Translational Regulation
11. Summary and Clinical Relevance

CONTENTS

Learning objectives

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

Explain why cells must regulate gene expression and how this differs between prokaryotes and eukaryotes. 2. Describe the levels at which gene expression can be regulated (transcription,
processing, translation, post-translation).
3. Explain the operon model of gene regulation in prokaryotes.
4. Describe the lac operon and distinguish between negative and positive control.
5. Describe the trp operon and explain attenuation. 6. Explain the role of chromatin remodeling and epigenetics in eukaryotic gene
regulation.
7. Describe the roles of transcription factors, enhancers, and silencers.
8. Identify post-transcriptional and translational mechanisms of gene regulation.
9. Relate defects in gene regulation to human diseases.

Introduction: Why Regulate Gene Expression?

All cells in an organism contain the same DNA (genome), but different cells express different genes.

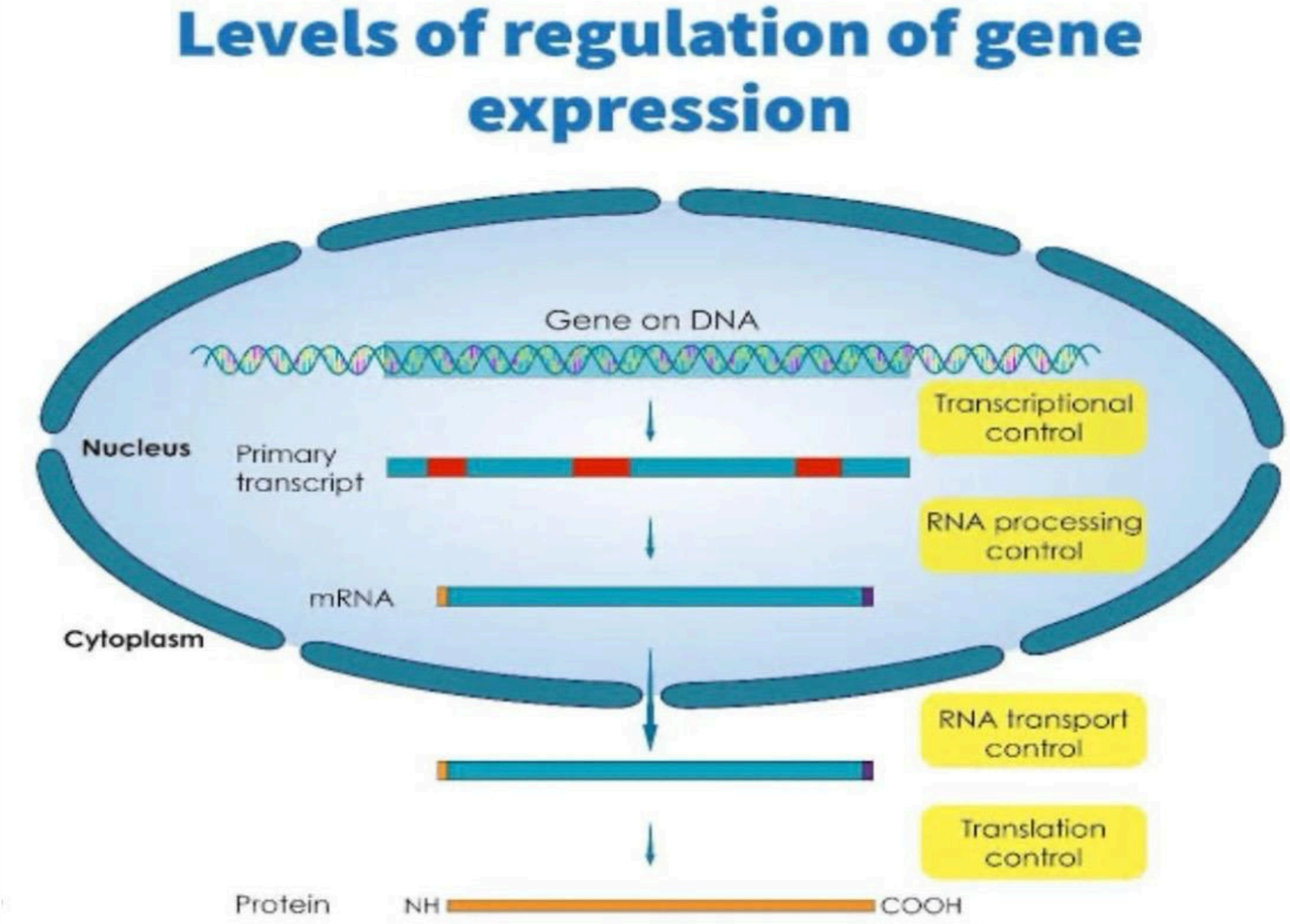
Reasons for regulating gene expression:

· Cell differentiation: A muscle cell and a neuron have the same DNA but express different proteins.· Response to environment: Cells must adapt to changes in nutrients, temperature, stress, and signals.· Efficiency: Producing only the proteins needed at a given time conserves energy and resources.· Development: Precise temporal and spatial expression patterns are essential for proper development.· Maintaining homeostasis: Cells must maintain a stable internal environment.

Key difference between prokaryotes and eukaryotes:

Prokaryotes: Gene expression is primarily regulated at the transcriptional level (operons). Transcription and translation are coupled.· Eukaryotes: Gene expression is regulated at multiple levels (chromatin, transcription, RNA processing, RNA stability, translation, post-translation). Transcription and translation are separated by the nuclear envelope.

Levels of Gene Expression Regulation



Regulation in Prokaryotes: The Operon Model

Prokaryotes regulate gene expression primarily at the level of transcription using operons.What is an operon?

A cluster of genes under the control of a single promoter and regulated together.

Operons allow coordinated expression of genes involved in the same metabolic pathway.

Components of an operon:

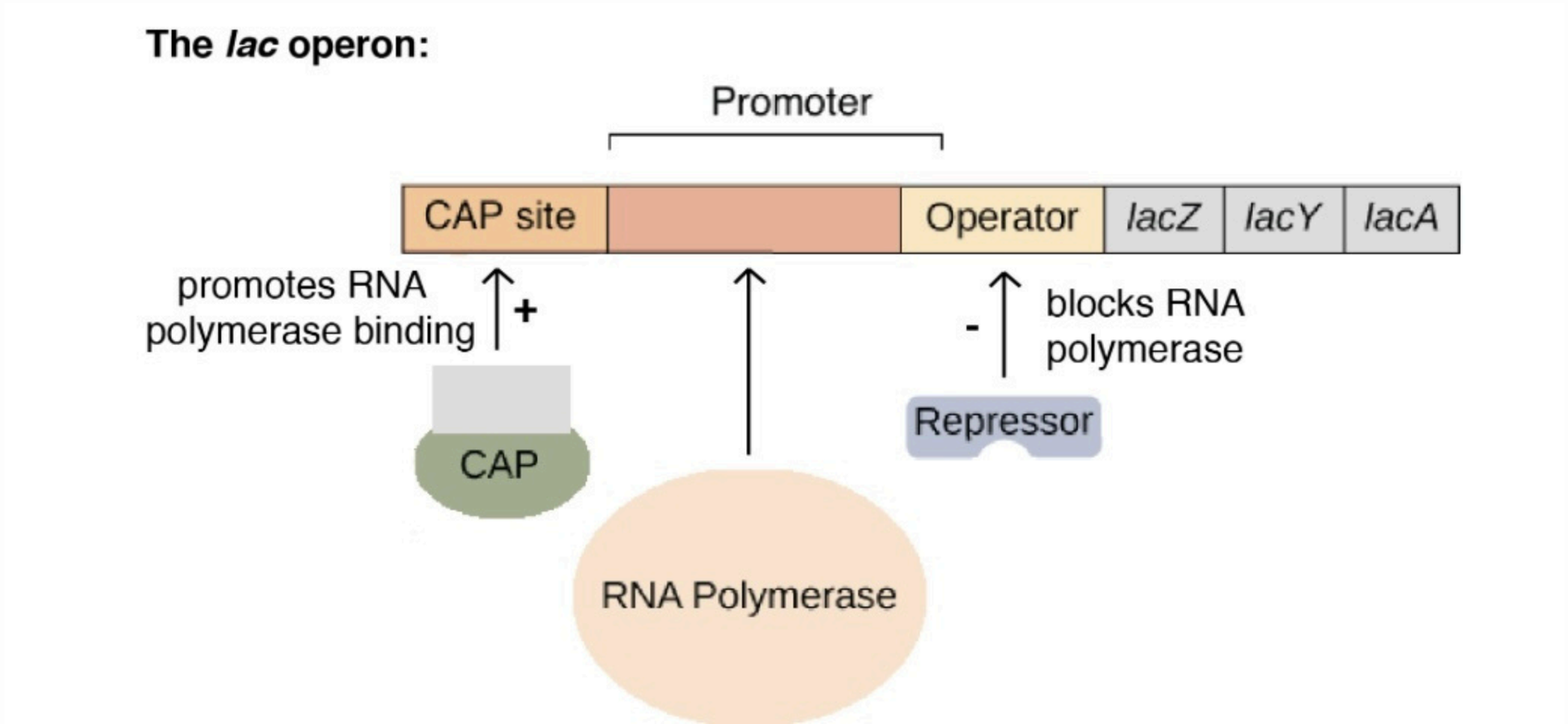
1. Promoter: RNA polymerase binding site.2. Operator: A DNA sequence where a repressor protein binds.3. Structural genes: The genes that encode enzymes or proteins.4. Regulatory gene: Encodes a repressor or activator protein (often located elsewhere in the genome).

Advantages of operons:

Efficient: One promoter controls multiple genes.
Coordinated: All enzymes for a pathway are produced together.
Economical: Genes are expressed only when needed.

The lac Operon: Negative and Positive Control

The lac operon in E. coli is one of the most well-studied examples of gene regulation.
Genes of the lac operon:
· lacZ: Encodes β-galactosidase (cleaves lactose into glucose and galactose).· lacY: Encodes lactose permease (transports lactose into the cell).· lacA: Encodes transacetylase.

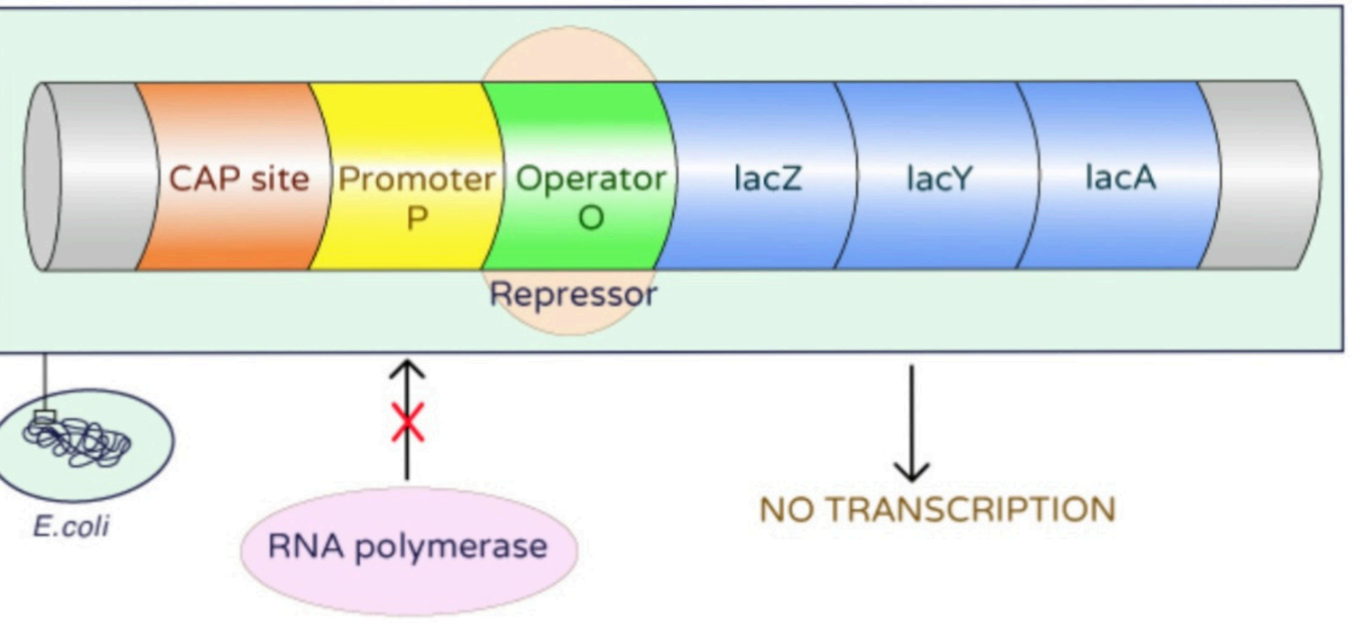


Lac Operon

ScienceFacts.net

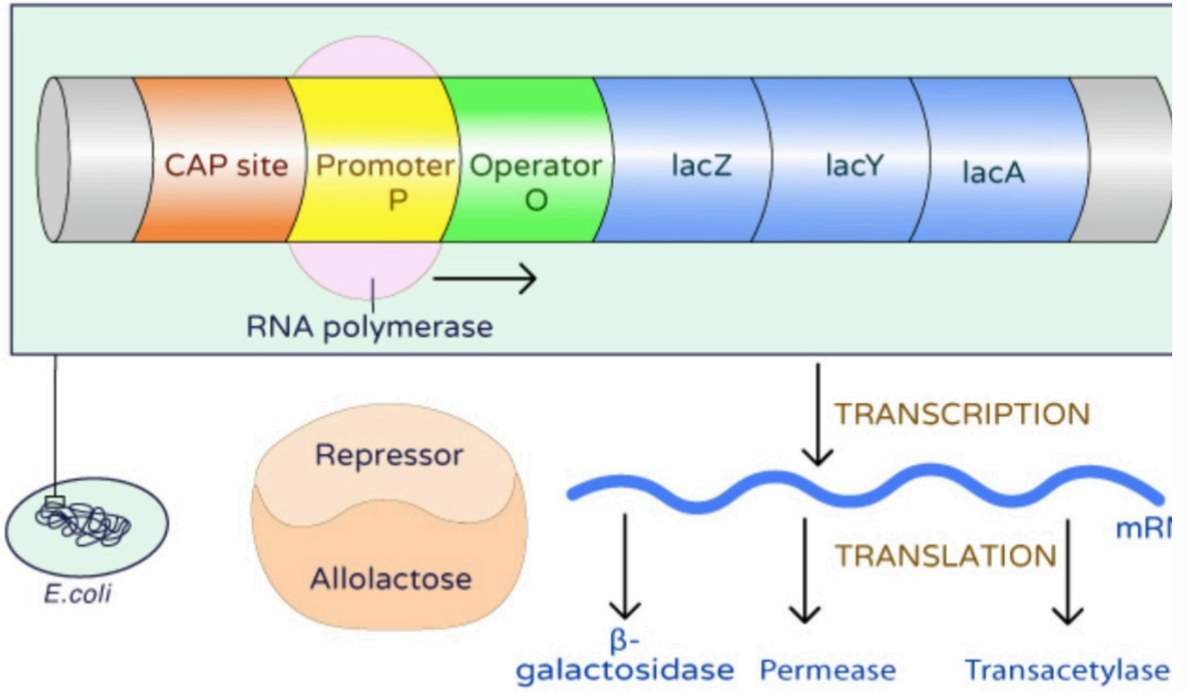
Absence of Lactose

The repressor binds tightly to the operator preventing RNA polymerase from binding to the promoter. No transcription of the structural genes occurs.



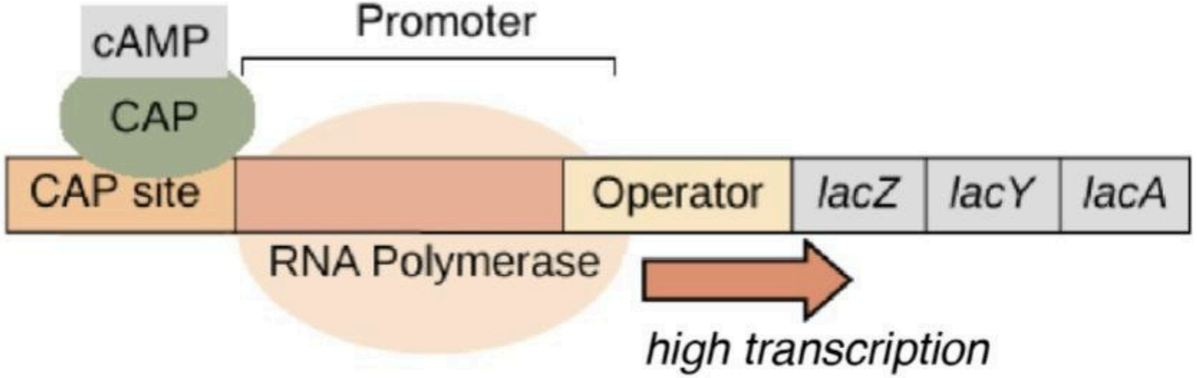
Presence of Lactose

Allolactose binds to the lac repressor, preventing the repressor from binding to the operator. Transcription of the structural genes occurs by RNA polymerase.



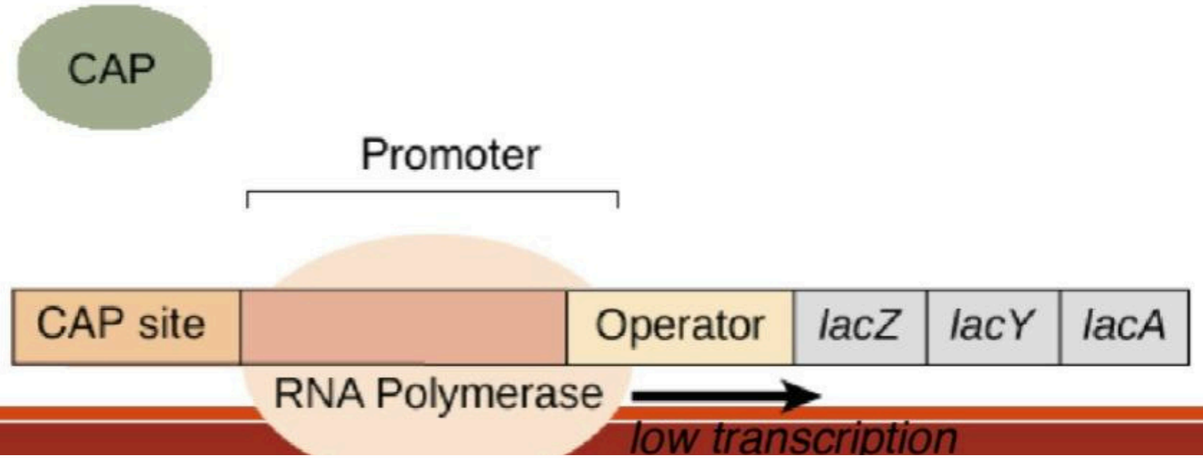
Low glucose:

When glucose levels are low, cAMP is produced. The cAMP attaches to CAP, allowing it to bind DNA. CAP helps RNA polymerase bind to the promoter, resulting in high levels of transcription.

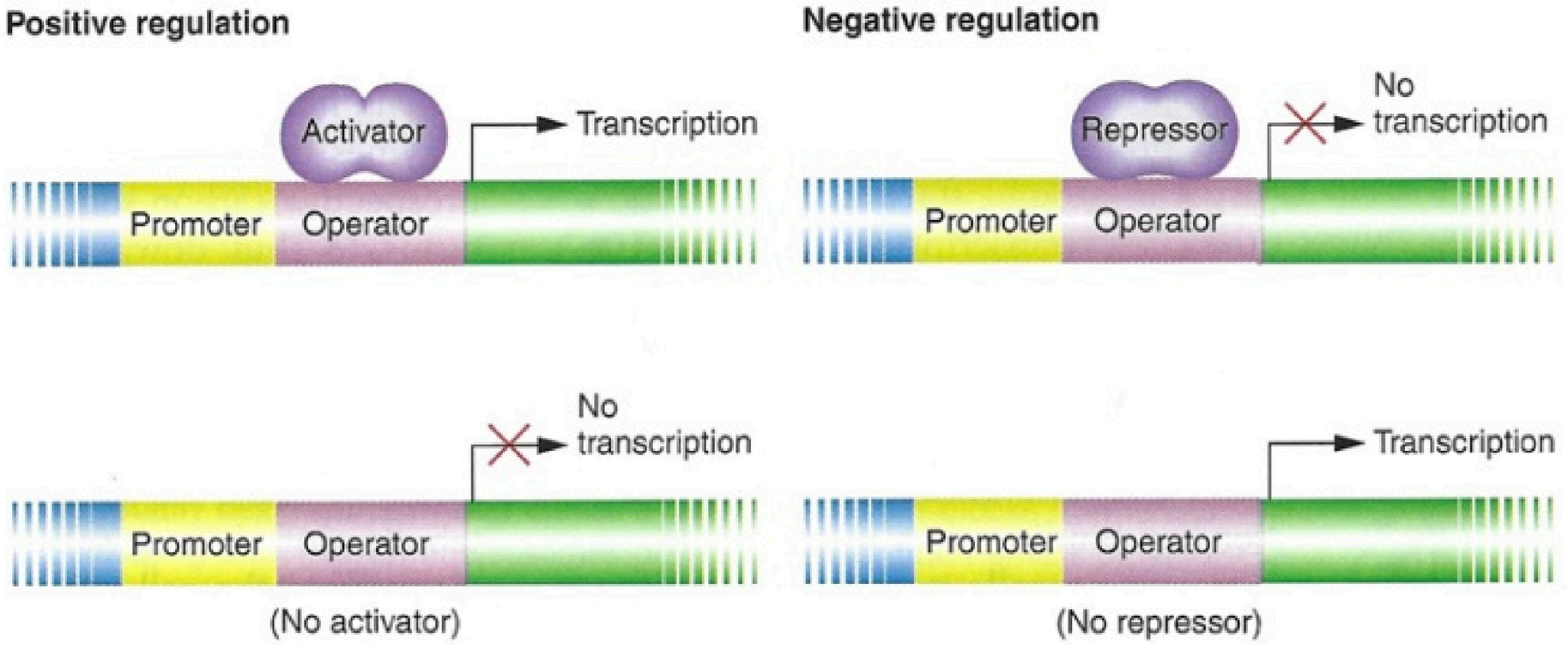


High glucose:

When glucose levels are high, no cAMP is made. CAP cannot bind DNA without cAMP, so transcription occurs only at a low level.



Positive and negative regulation



The trp Operon: Repression and Attenuation

The trp operon in E. coli is an example of an anabolic operon that is regulated by the end product of its pathway.

Genes of the trp operon:

Five structural genes (trpE, trpD, trpC, trpB, trpA) that encode enzymes for tryptophan biosynthesis.

The trp Operon: Repression and Attenuation

REPRESSION:

· In the absence of tryptophan, the trp repressor (encoded by trpR) is inactive and cannot bind to the operator. Transcription occurs.
· In the presence of tryptophan, tryptophan acts as a corepressor, binding to the repressor and activating it. The active repressor binds to the operator and blocks transcription.

ATTENUATION:

A second level of regulation specific to the trpoperon.A short leader sequence at the 5' end of the mRNA contains two tryptophan codons. When tryptophan is abundant, the ribosome translates the leader sequence quickly, allowing the RNA to form a termination hairpin (3-4 stem-loop). Transcription stops early (attenuation). When tryptophan is scarce, the ribosome stalls at the tryptophan codons, allowing the RNA to form an antitermination hairpin (2-3 stem-loop). Transcription continues through the structural genes.

Regulation in Eukaryotes: An Overview

Eukaryotic gene regulation is more complex and occurs at multiple levels.

Key features of eukaryotic gene regulation:

1. Chromatin structure: DNA is packaged with histones; accessibility must be regulated.
2. Transcription: Controlled by transcription factors, enhancers, silencers, and promoters.
3. RNA processing: Alternative splicing allows one gene to produce multiple proteins.
4. RNA stability: miRNAs and RNA-binding proteins regulate mRNA half-life.
5. Translation: Initiation can be regulated by phosphorylation of initiation factors.
6. Post-translational modification: Proteins can be activated, inhibited, or degraded.

Key difference from prokaryotes:

· Eukaryotes do not typically use operons. Instead, each gene has its own promoter and regulatory elements.

· Genes involved in the same pathway are often scattered across the genome but regulated by shared transcription factors.

Chromatin Remodeling and Epigenetic Regulation

1. HISTONE MODIFICATION:

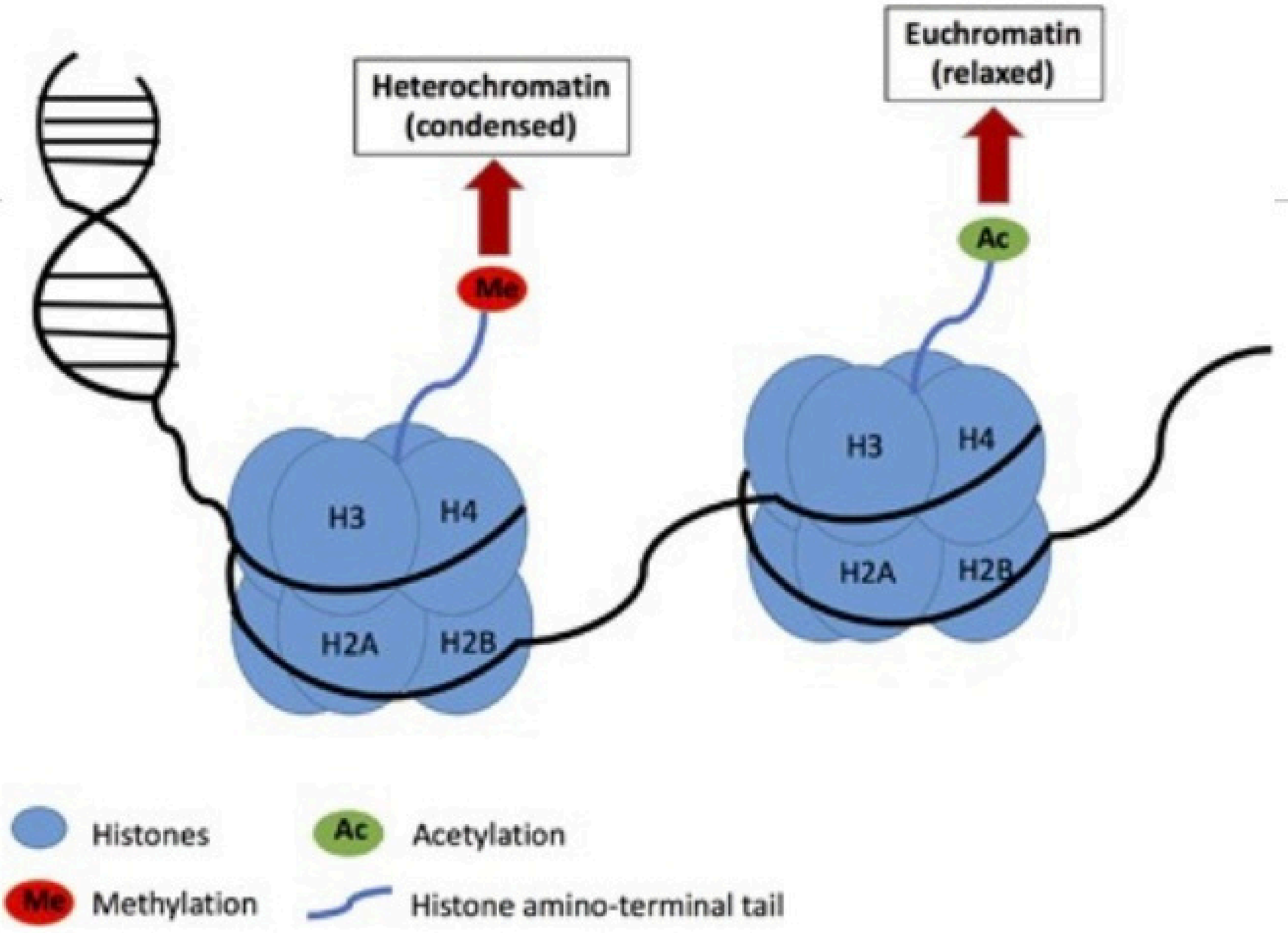
· Histone acetylation: Acetyl groups are added to lysine residues in histone tails. This loosens chromatin structure and activates transcription.· Histone methylation: Can activate or repress transcription depending on the specific residue modified (e.g., H3K4me3 activates; H3K27me3 represses).· Histone phosphorylation: Involved in chromatin condensation and DNA repair.

2. DNA METHYLATION:

· Methyl groups are added to cytosine bases (usually in CpG islands) by DNA methyltransferases (DNMTs).· DNA methylation typically represses transcription by recruiting proteins that compact chromatin or block transcription factor binding.· DNA methylation patterns can be inherited across cell divisions (epigenetic inheritance).

Chromatin Remodeling and Epigenetic Regulation

3. Chromatin remodeling complexes:
Protein complexes (e.g., SWI/SNF) use ATP to slide, eject, or restructure nucleosomes, making DNA accessible or inaccessible. Epigenetics: Heritable changes in gene expression that do not involve changes in DNA sequence.


Heterochromatin
(condensed)
Euchromatin
(relaxed)
Me
Ac
H3
H4
H2A
H2B
H3
H4
H2A
H2B
Histones
Acetylation
Methylation
Histone amino-terminal tail

Transcriptional Regulation: Transcription Factors and Enhancers

Eukaryotic transcription is controlled by a complex interplay of proteins and DNA sequences.

1. General transcription factors (GTFs):

· Required for RNA polymerase II to bind to the promoter (e.g., TFIIA, TFIIB, TFIID, TFIIE, TFIIH).· TFIID binds to the TATA box via the TATA-binding protein (TBP).

2. Specific transcription factors:

· Bind to specific DNA sequences (response elements) in enhancers or promoters.· Can be activators (increase transcription) or repressors (decrease transcription).· Often regulated by external signals (e.g., hormones, growth factors) via signal transduction pathways.· Common DNA-binding domains: helix-turn-helix, zinc finger, leucine zipper, helix-loop-helix.

Transcriptional Regulation: Transcription Factors and Enhancers

3. Enhancers and silencers:

· Enhancers: DNA sequences that can be located far from the promoter (upstream, downstream, or within introns). They increase transcription by looping to interact with the promoter.

· Silencers: DNA sequences that repress transcription.

· Insulators: Boundaries that prevent enhancers from acting on the wrong genes.

4. Combination control:

The specific combination of transcription factors present in a cell determines which genes are expressed. This is the basis of cell differentiation.

Post-Transcriptional Regulation

1.ALTERNATIVE SPLICING:

- Different combinations of exons are joined together to produce different mRNA variants from the same gene.
- Allows one gene to encode multiple protein isoforms.
- Regulated by splicing factors (e.g., SR proteins, hRNPs).
- Example: The calcitonin gene produces calcitonin in thyroid cells and CGRP in neurons via alternative splicing.

2. RNA EDITING:

- Changes to the nucleotide sequence of RNA after transcription (e.g., C → U, A → I).
- Can alter the coding sequence and protein function.
- Example: Apolipoprotein B (ApoB) is edited in the intestine to produce a shorter form (ApoB-48) versus the liver form (ApoB-100).

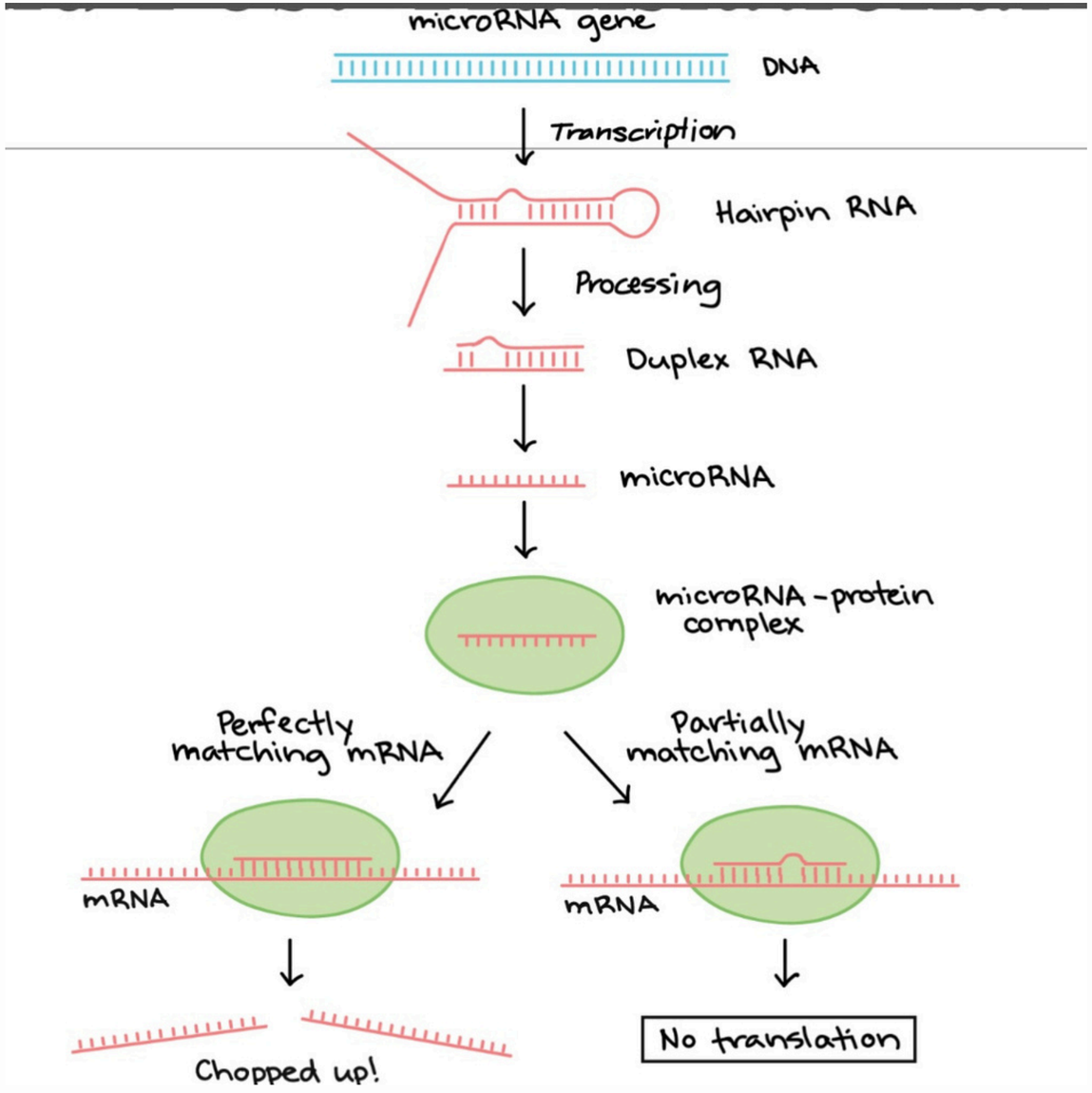
3. MRNA STABILITY:

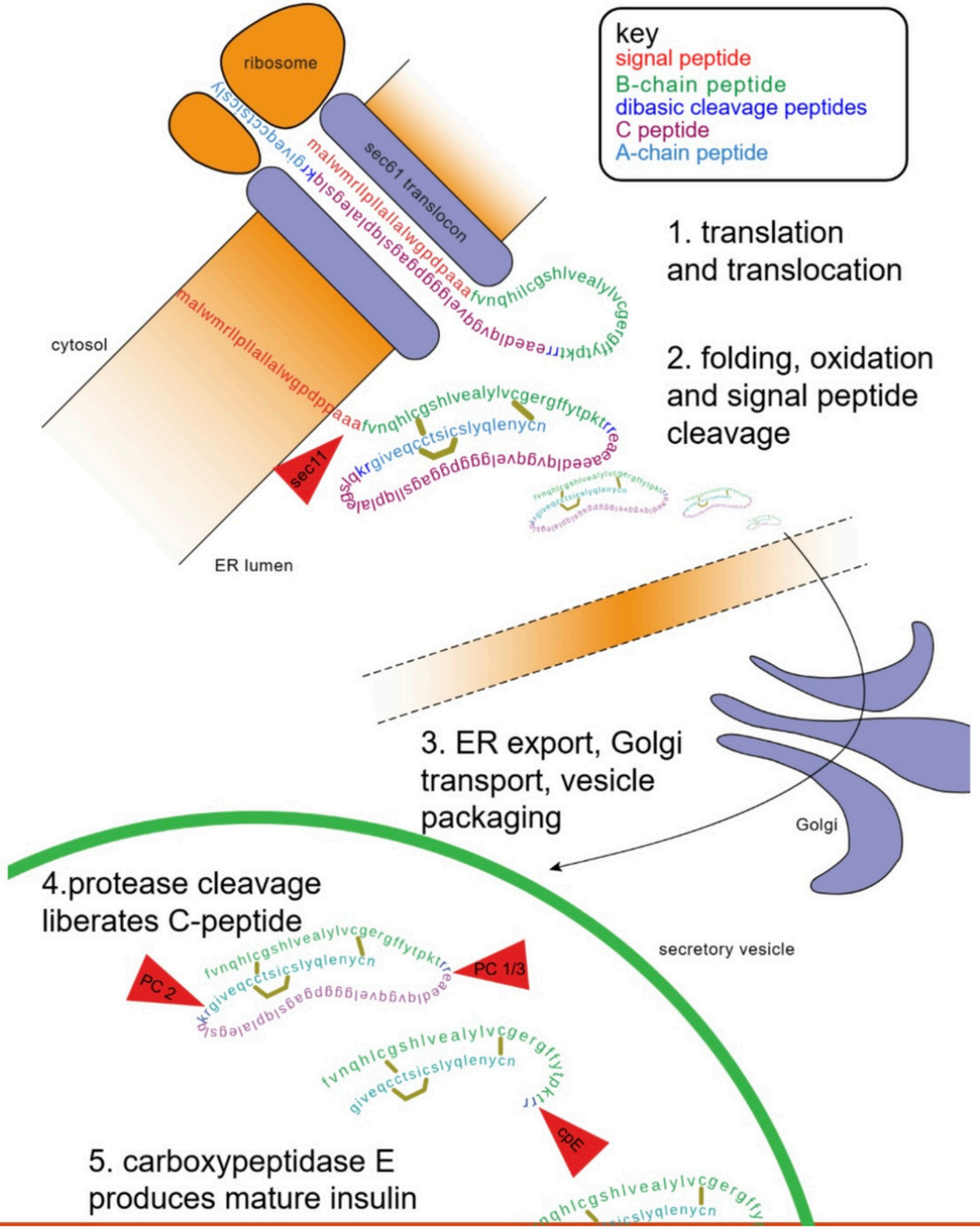
The half-life of mRNA determines how much protein is produced.
miRNAs (microRNAs) bind to mRNA and promote degradation or inhibit translation.
RNA-binding proteins can stabilize or destabilize mRNA.
Example: Transferrin mRNA is stabilized when iron levels are low.

4. RNA INTERFERENCE (RNAI):

- Small interfering RNAs (siRNAs) and miRNAs can silence gene expression by degrading mRNA or blocking translation.

Translational and Post-Translational Regulation




key
signal peptide
B-chain peptide
dibasic cleavage peptides
C peptide
A-chain peptide
ribosome
sec61 translocon
cytosol
ER lumen
sec11
1. translation and translocation
2. folding, oxidation and signal peptide cleavage
3. ER export, Golgi transport, vesicle packaging
Golgi
4.protease cleavage liberates C-peptide
PC 2
PC 1/3
secretory vesicle
cpE
5. carboxypeptidase E produces mature insulin

Summary: The Complete Picture

· Gene expression is regulated to ensure that cells produce the right proteins at the right time.
· Prokaryotes primarily regulate transcription via operons (e.g., lac and trp operons).
· Eukaryotes regulate gene expression at multiple levels: chromatin structure, transcription, RNA processing, RNA stability, translation, and post-translational modification.
· Epigenetic mechanisms (histone modification, DNA methylation) play a key role in eukaryotic gene regulation.
· Transcription factors, enhancers, and silencers control eukaryotic transcription.
· Post-transcriptional mechanisms (alternative splicing, miRNA) add another layer of regulation.

Clinical Relevance:

· Cancer: Many cancers are caused by mutations in genes that regulate cell growth (oncogenes and tumor suppressor genes). For example, mutations in the p53 gene (a transcription factor) lead to uncontrolled cell division.
· Fragile X Syndrome: Caused by hypermethylation and silencing of the FMR1 gene.
· Rett Syndrome: Caused by mutations in MECP2, a gene involved in DNA methylation-dependent gene repression.
· Chronic Myeloid Leukemia (CML): Caused by a chromosomal translocation that creates the BCR-ABL fusion gene, leading to constitutive gene expression. Targeted by the drug imatinib.
· Antibiotic resistance: Bacteria can regulate gene expression to survive antibiotic exposure (e.g., efflux pumps).

COMMON SYMPTOMS OF RETT SYNDROME



Slowed head growth



Difficulty communicating



Loss of hand skills



Uncontrolled, repetitive hand movements



Seizures



Abnormal spine curvature



Sleep problems



Behavioral issues

Student task

Task 1 - Check your understanding:

1. Why is gene regulation important for cellular differentiation?
2. What is an operon? What are its components?
3. Explain how the lac operon is regulated by both lactose and glucose.
4. What is attenuation in the trp operon?
5. What is the difference between histone acetylation and DNA methylation in terms of gene expression?
6. What are enhancers and how do they work?
7. What is alternative splicing? Give an example.
8. How do miRNAs regulate gene expression?

Task 2 - Complete the pathway:

Complete the regulation of the lac operon:

· Lactose absent, glucose present → Repressor bound → (1) __

· Lactose present, glucose present → Repressor inactive, CAP not bound → (2) __

· Lactose present, glucose absent → Repressor inactive, CAP bound → (3) _

Then explain:1. Why is the lac operon not expressed when glucose is present?2. What would happen if the lacI gene were mutated and produced a non-functional repressor?

Conclusion

· Regulation of gene expression is essential for cellular differentiation, adaptation, and homeostasis.
· Prokaryotes regulate gene expression primarily through operons, which allow coordinated expression of genes in a pathway.
· The lac operon is a classic example of negative and positive control.
· The trp operon illustrates repression and attenuation.
· Eukaryotes regulate gene expression at multiple levels, including chromatin structure, transcription, RNA processing, RNA stability, translation, and post-translational modification.
· Understanding gene regulation is crucial for understanding development, disease, and the mechanisms of drug action.

References

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