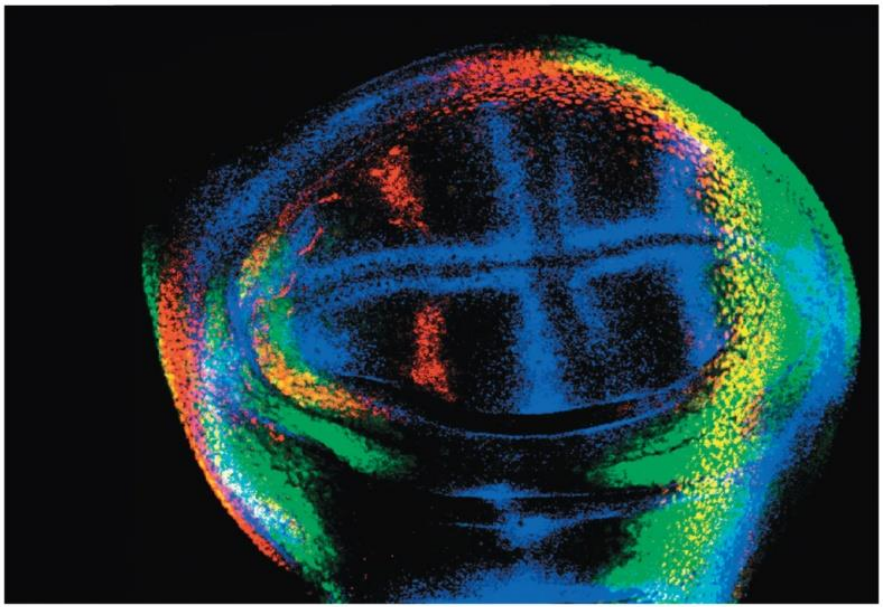
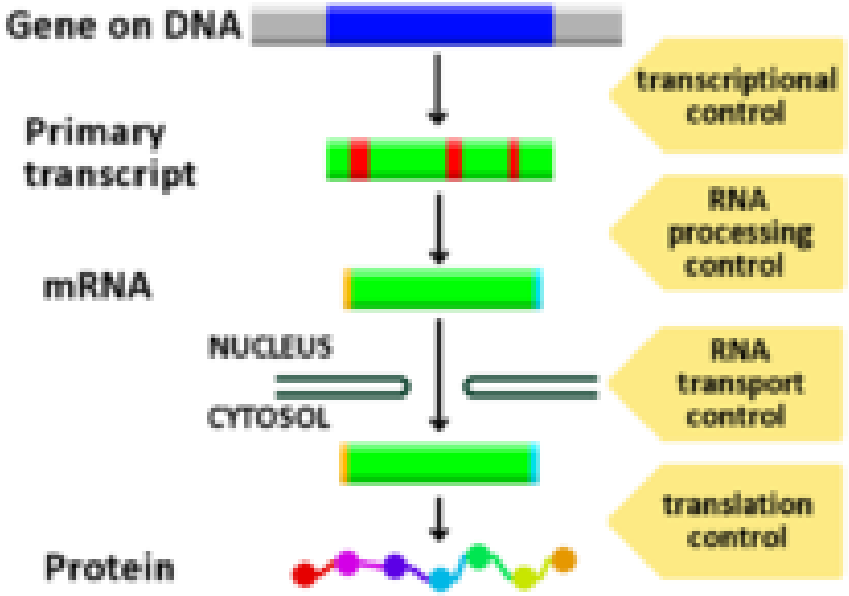
# NOTES: CH 18 – part 1
# Regulation of Gene Expression: Prokaryotes vs. Eukaryotes



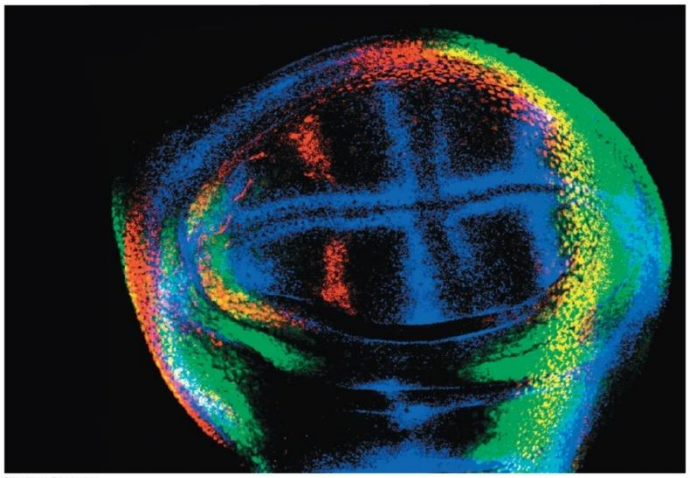
# Regulation of Gene Expression:

- Both prokaryotes & eukaryotes must alter their patterns of gene expression in response to **changes in environmental conditions**;
- Multicellular eukaryotes must also develop and maintain **multiple cell types**

  -each cell type contains the **same genome** but expresses **a different subset of genes**…*how is this accomplished??*

# Regulation of Gene Expression:

- Gene expression in both eukaryotes & prokaryotes is often regulated at the stage of **TRANSCRIPTION** (DNA ➔ mRNA)
- we now know that RNA molecules play many roles in regulating gene expression

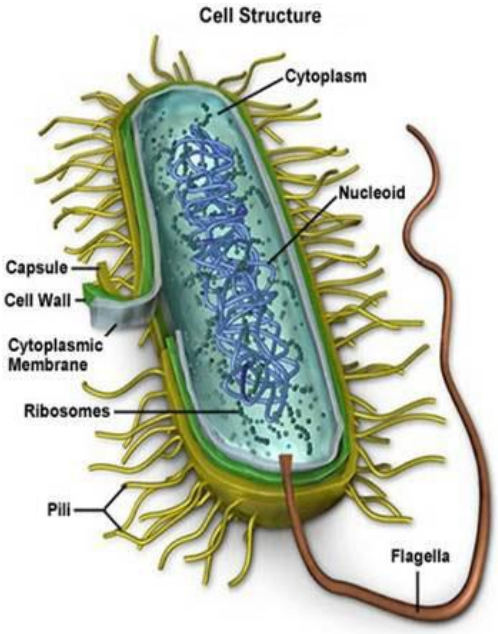


# 18.1: BACTERIA

- bacterial cells that can conserve resources and energy have a selective advantage over cells that are unable to do so…
- thus, natural selection has **favored** bacteria that express ONLY the genes whose products are needed by the cell at any given moment…

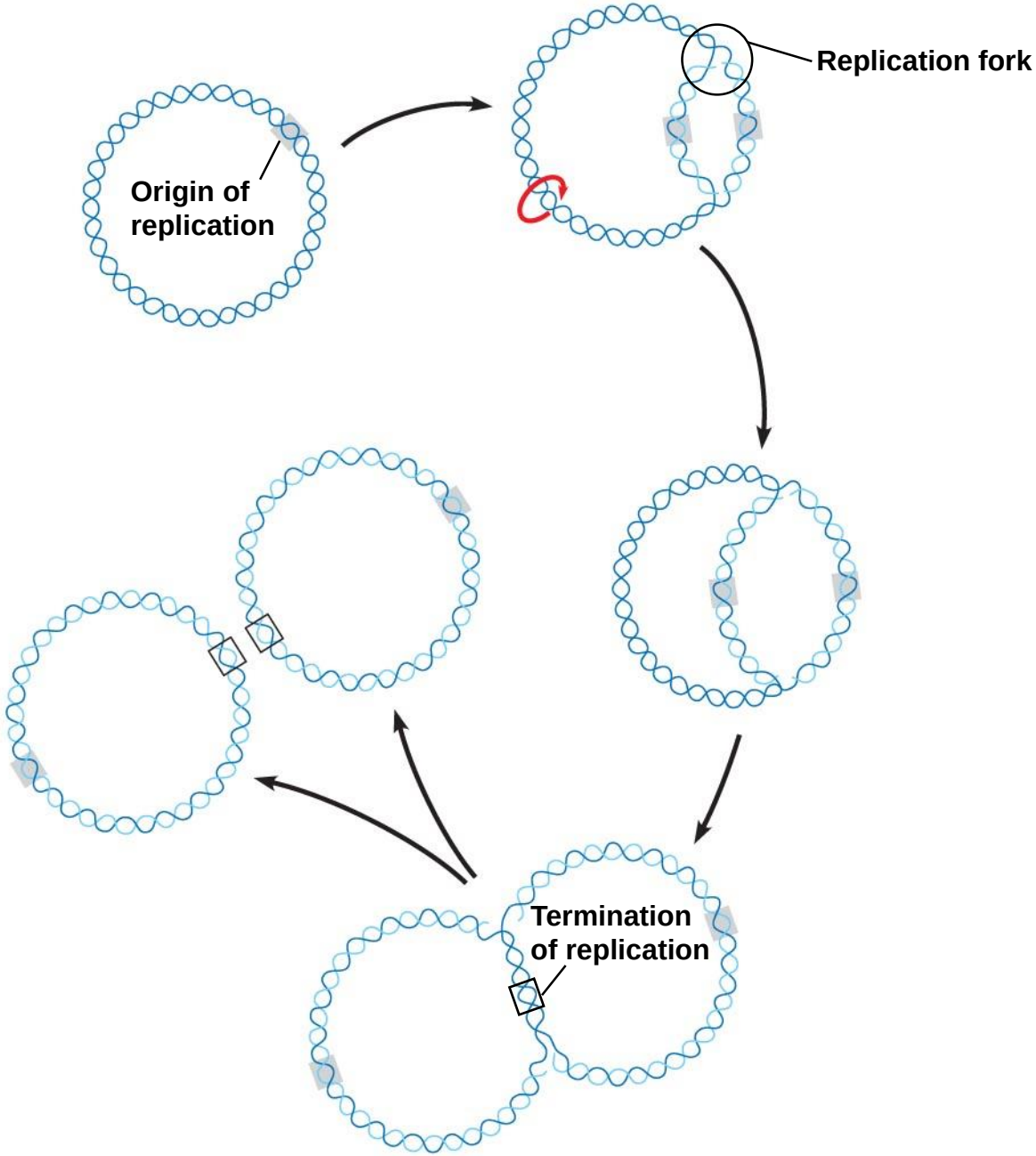
# Rapid reproduction, mutation, and genetic recombination contribute to the genetic diversity of bacteria

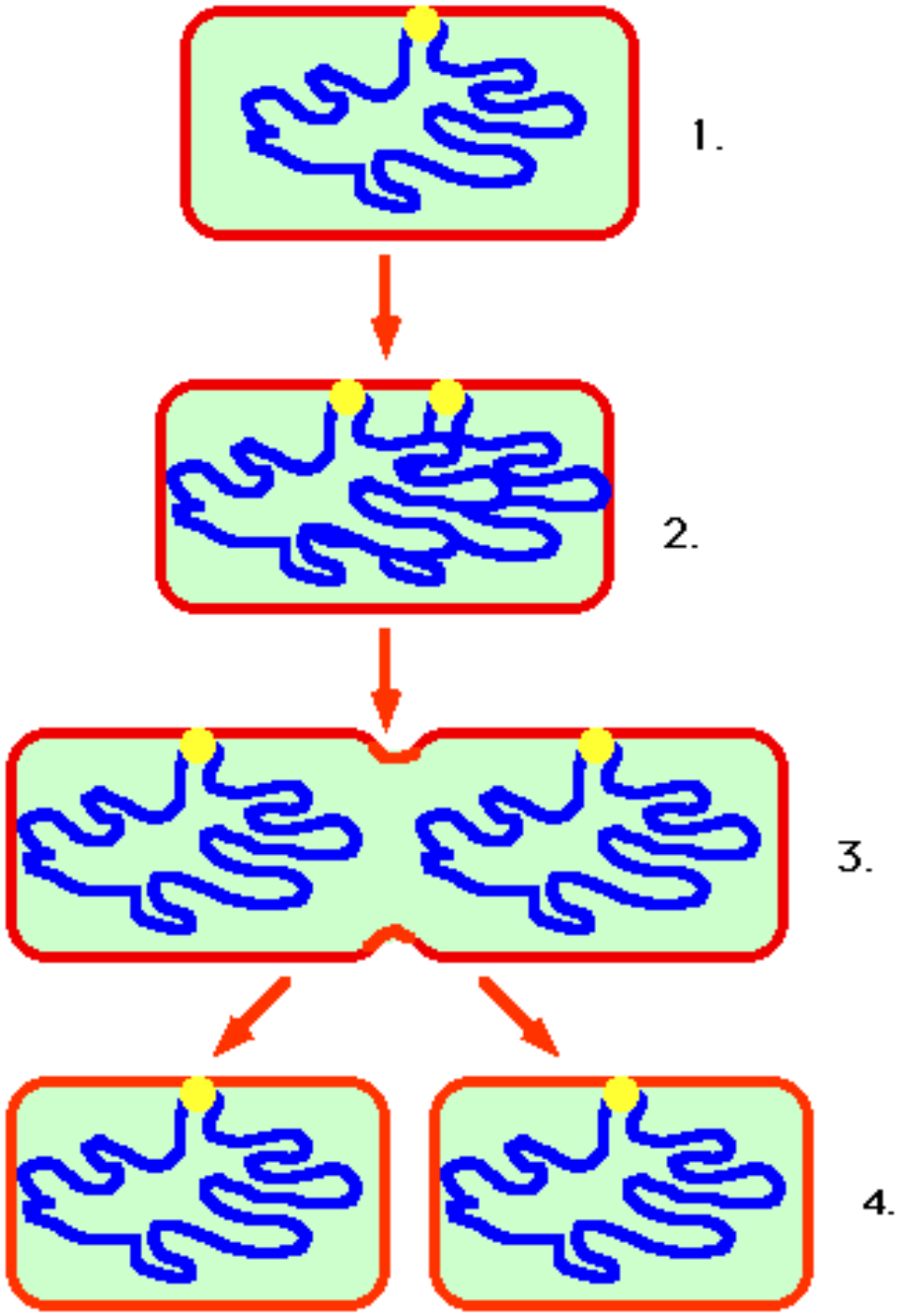
- Bacteria allow researchers to investigate molecular genetics in the simplest true organisms
- The well-studied intestinal bacterium ***Escherichia coli (E. coli)*** is "the laboratory rat of molecular biology"



# The Bacterial Genome and Its Replication:

- The bacterial chromosome is usually a circular DNA molecule with few associated proteins
- Many bacteria also have **PLASMIDS**, smaller circular DNA molecules that can replicate independently of the chromosome
- Bacterial cells divide by **BINARY FISSION**, which is preceded by replication of the chromosome




1.
2.
3.
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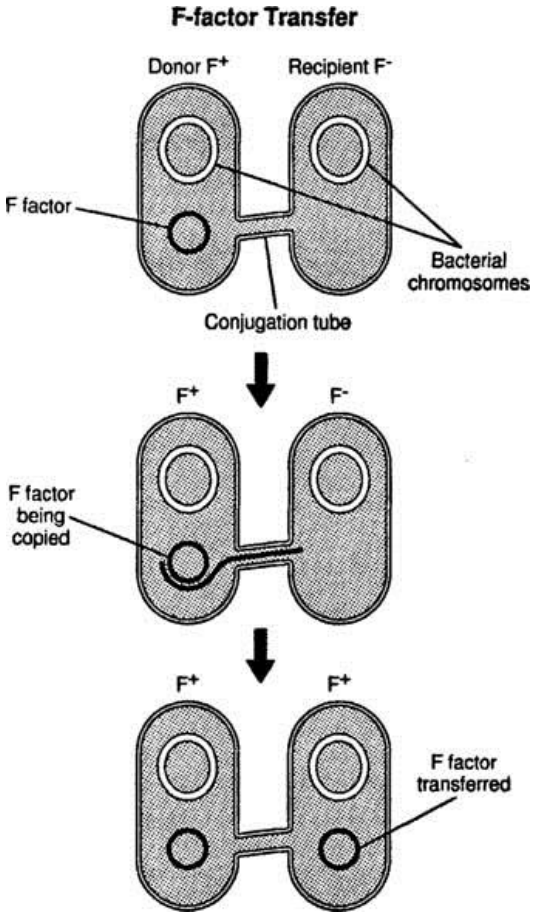
# Mutation and Genetic Recombination as Sources of Genetic Variation

- Since bacteria can reproduce rapidly, new mutations quickly increase genetic diversity
- More genetic diversity arises by recombination of DNA from two different bacterial cells

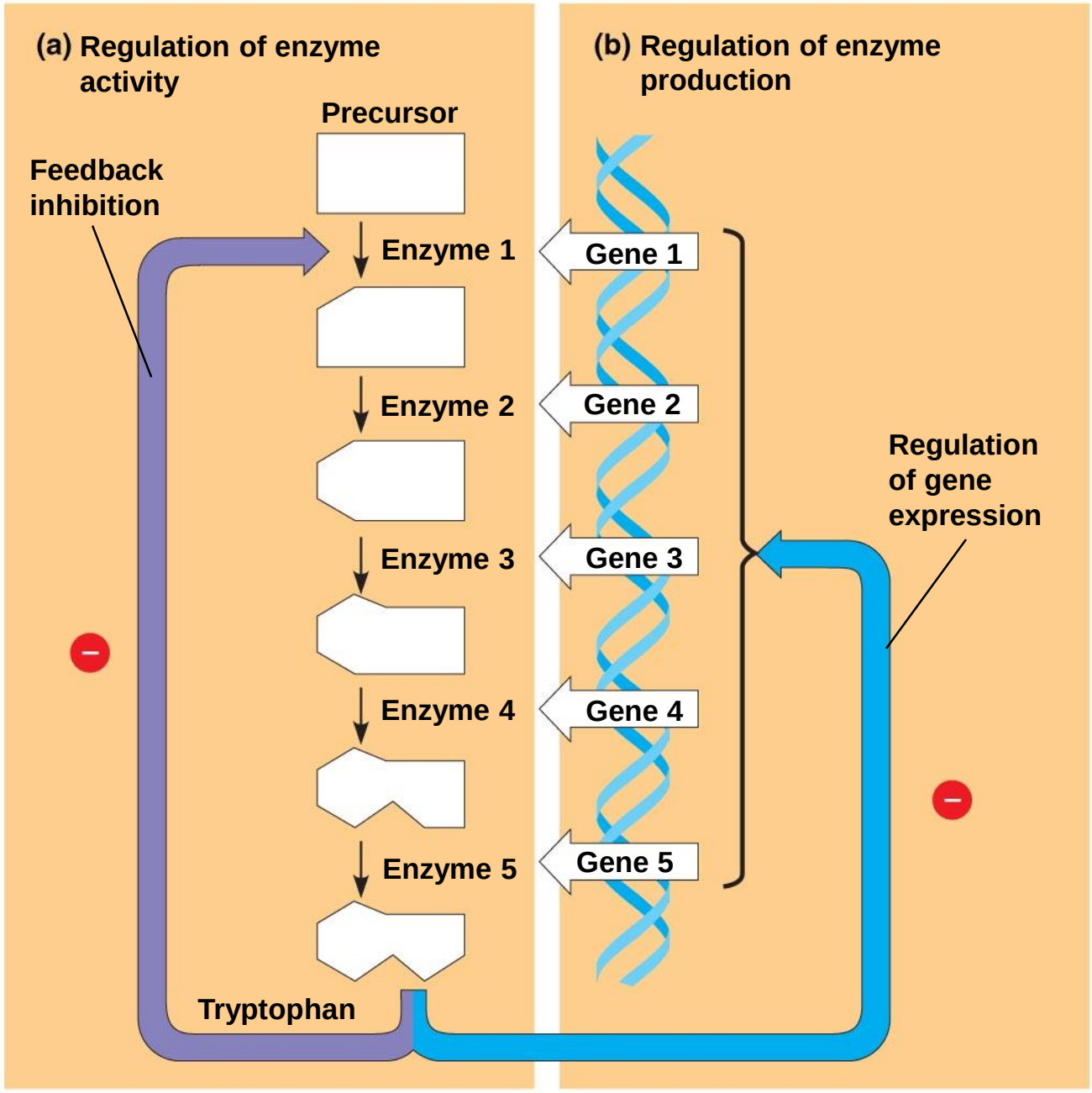


# Individual bacteria respond to environmental change by regulating their gene expression

- A bacterium can tune its metabolism to the changing environment and food sources
- This metabolic control occurs on two levels:

1) Adjusting activity of metabolic enzymes

2) Regulating genes that encode metabolic enzymes

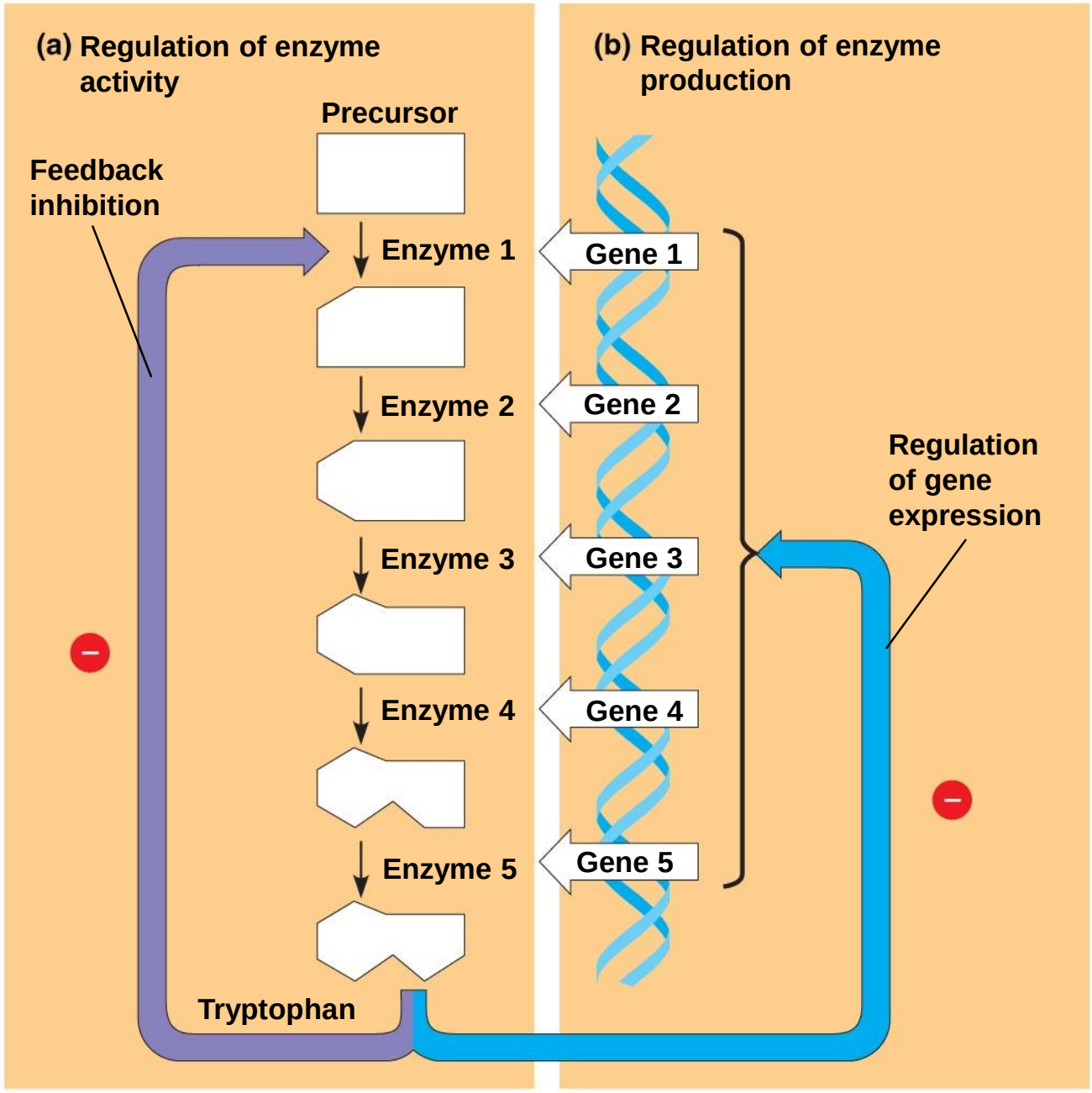


# **EXAMPLE**:

- consider an individual E. coli cell living in the constantly-changing environment of a human colon…it depends on the eating habits of its host!!
- if, for example, the environment is lacking in the amino acid tryptophan, which it needs to survive, the cell responds by activating a metabolic pathway that makes tryptophan from another compound…

# **EXAMPLE**:

- later, if the human host eats a tryptophan-rich meal, the bacterial cell stops producing tryptophan, thus saving itself from wasting resources to produce a substance that is readily available from its surroundings…
- this is one example of how bacteria respond and fine-tune their metabolism to a changing environment!



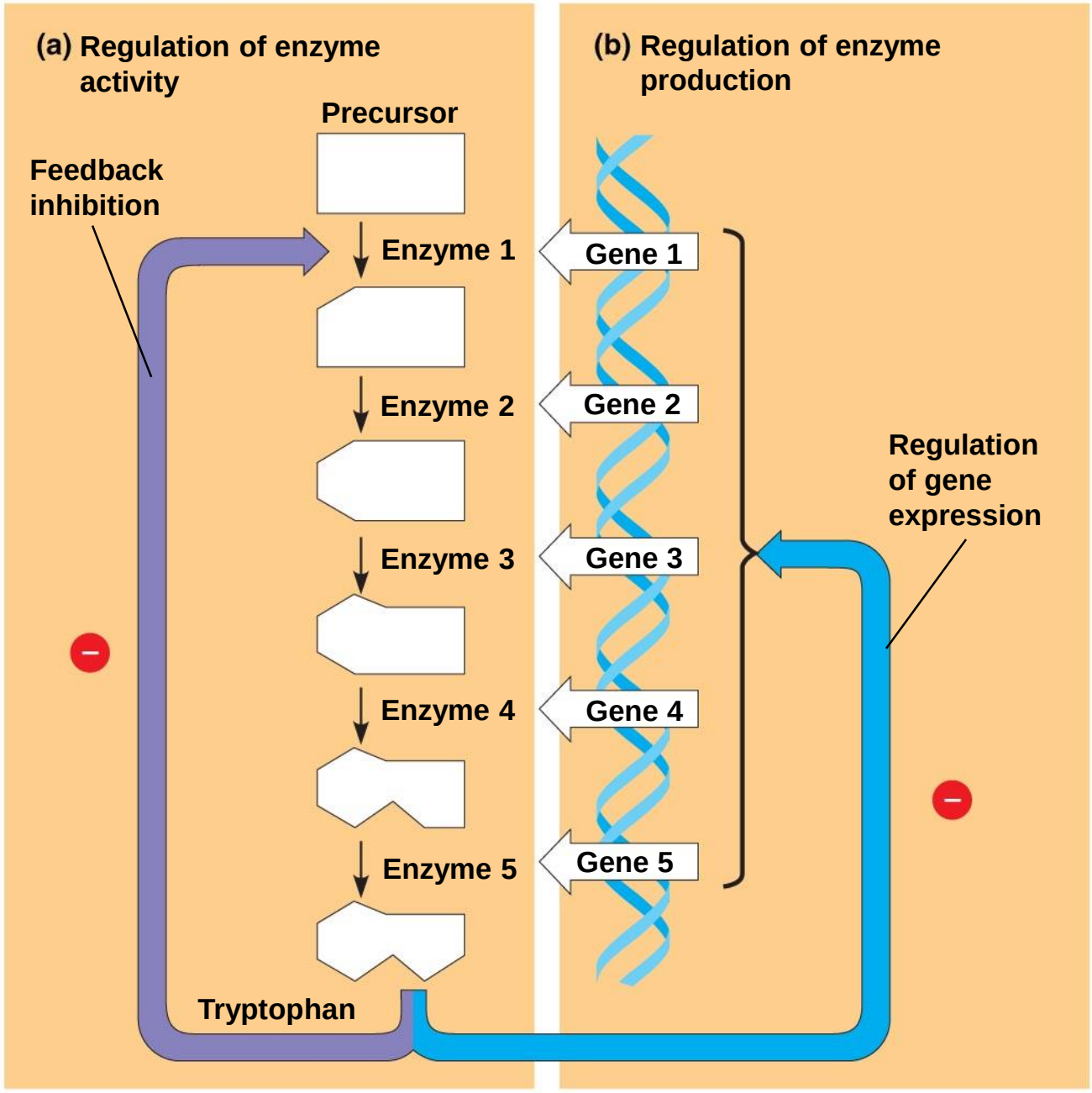
# Individual bacteria respond to environmental change by regulating their gene expression

- A bacterium can tune its metabolism to the changing environment and food sources
- This metabolic control occurs on two levels:

1) Adjusting activity of metabolic enzymes

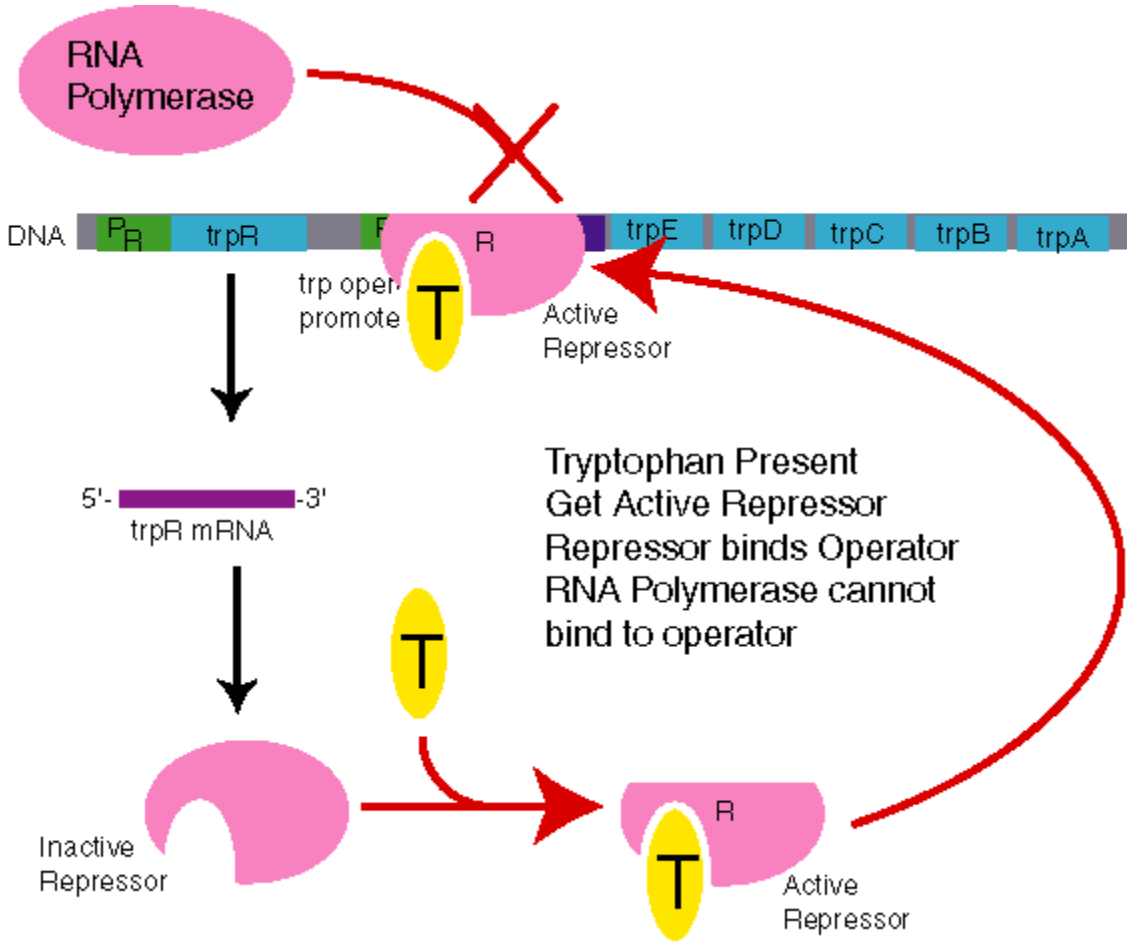
(**Allosteric regulation**; short-term feedback inhibition)

2) Regulating genes that encode metabolic enzymes ***(occurs at the level of transcription!...how?...OPERONS!!)***



# Operons: The Basic Concept

- In bacteria, genes are often clustered into operons, composed of:
  - An **OPERATOR**, an "on-off" switch
  - A **PROMOTER**
  - **GENES** for metabolic enzymes
- An operon can be switched off by a protein called a **REPRESSOR**
- A **corepressor** is a small molecule that cooperates with a repressor to switch an operon off


RNA
Polymerase
DNA
$P_R$
trpR
R
trpE
trpD
trpC
trpB
trpA
trp oper
promote
T
Active
Repressor
5'-
-3'
trpR mRNA
Tryptophan Present
Get Active Repressor
Repressor binds Operator
RNA Polymerase cannot
bind to operator
T
Inactive
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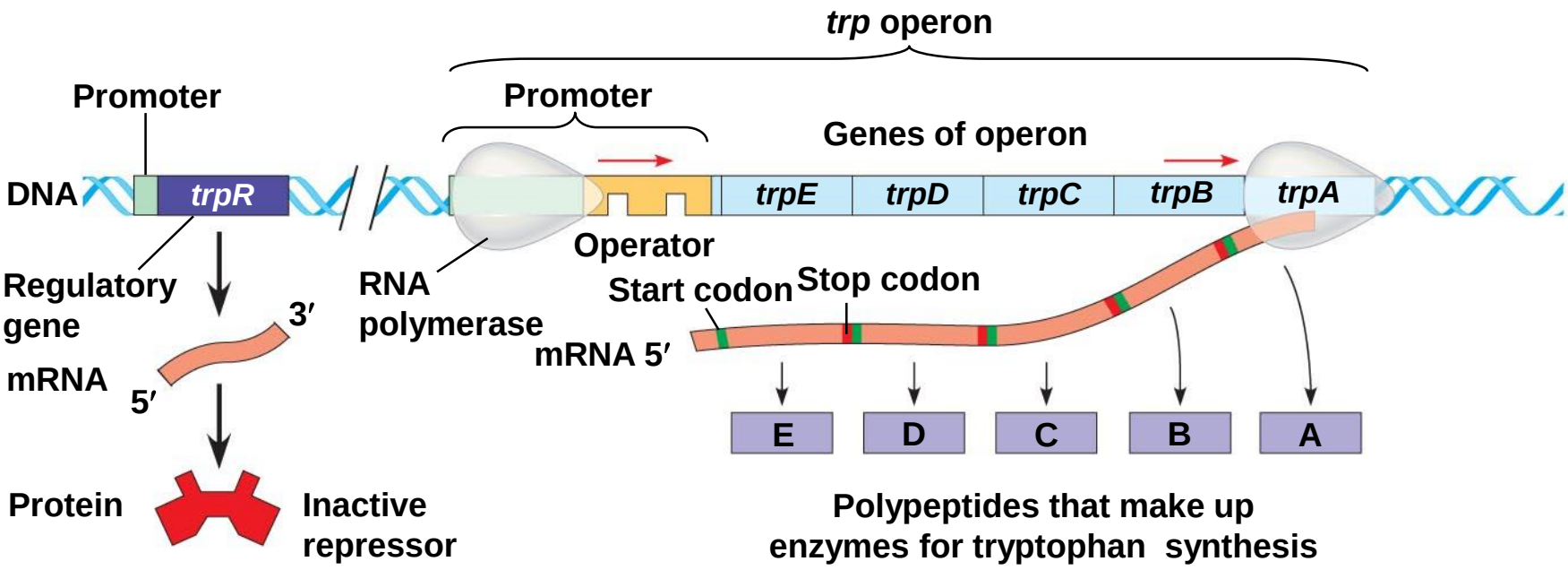
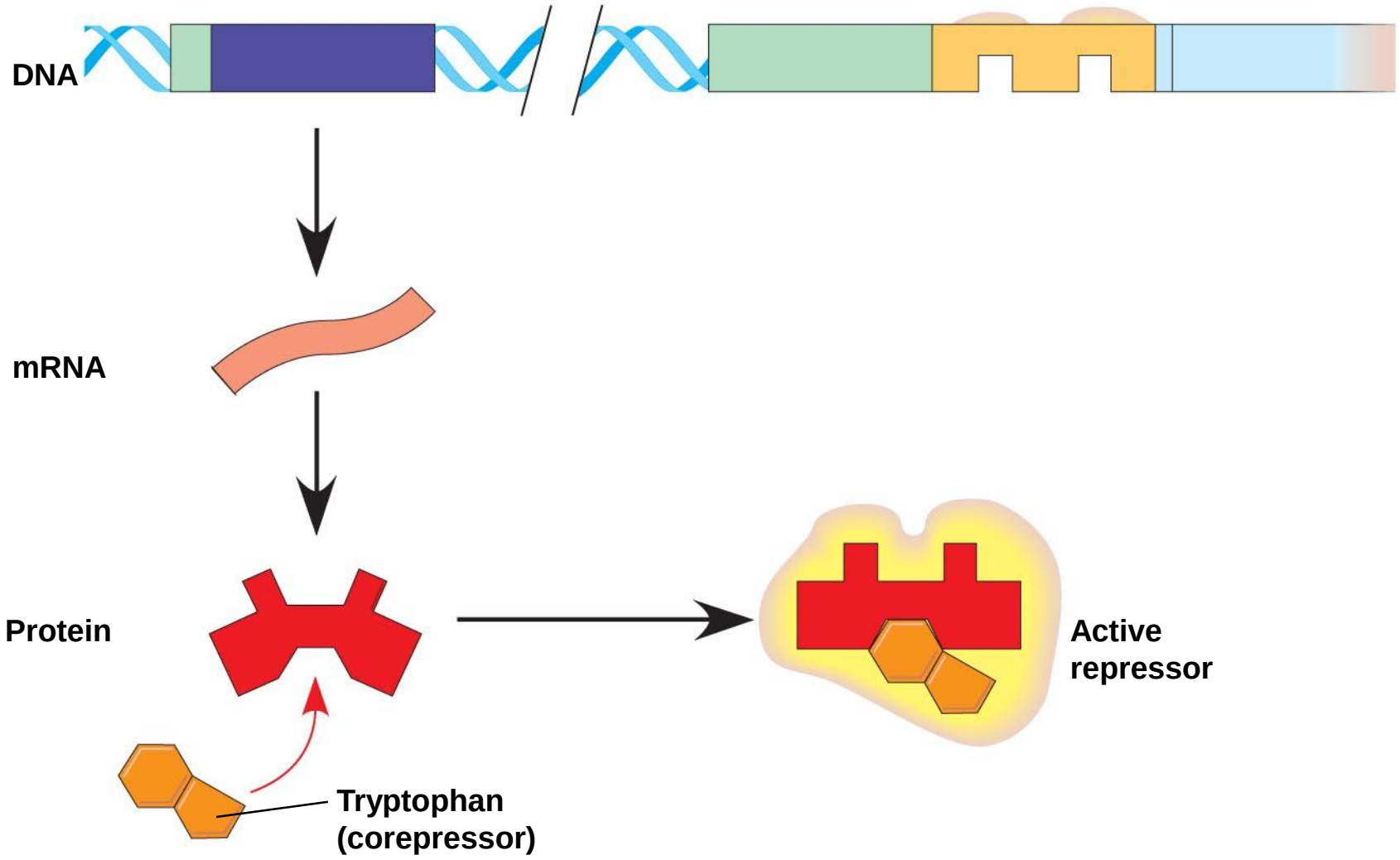
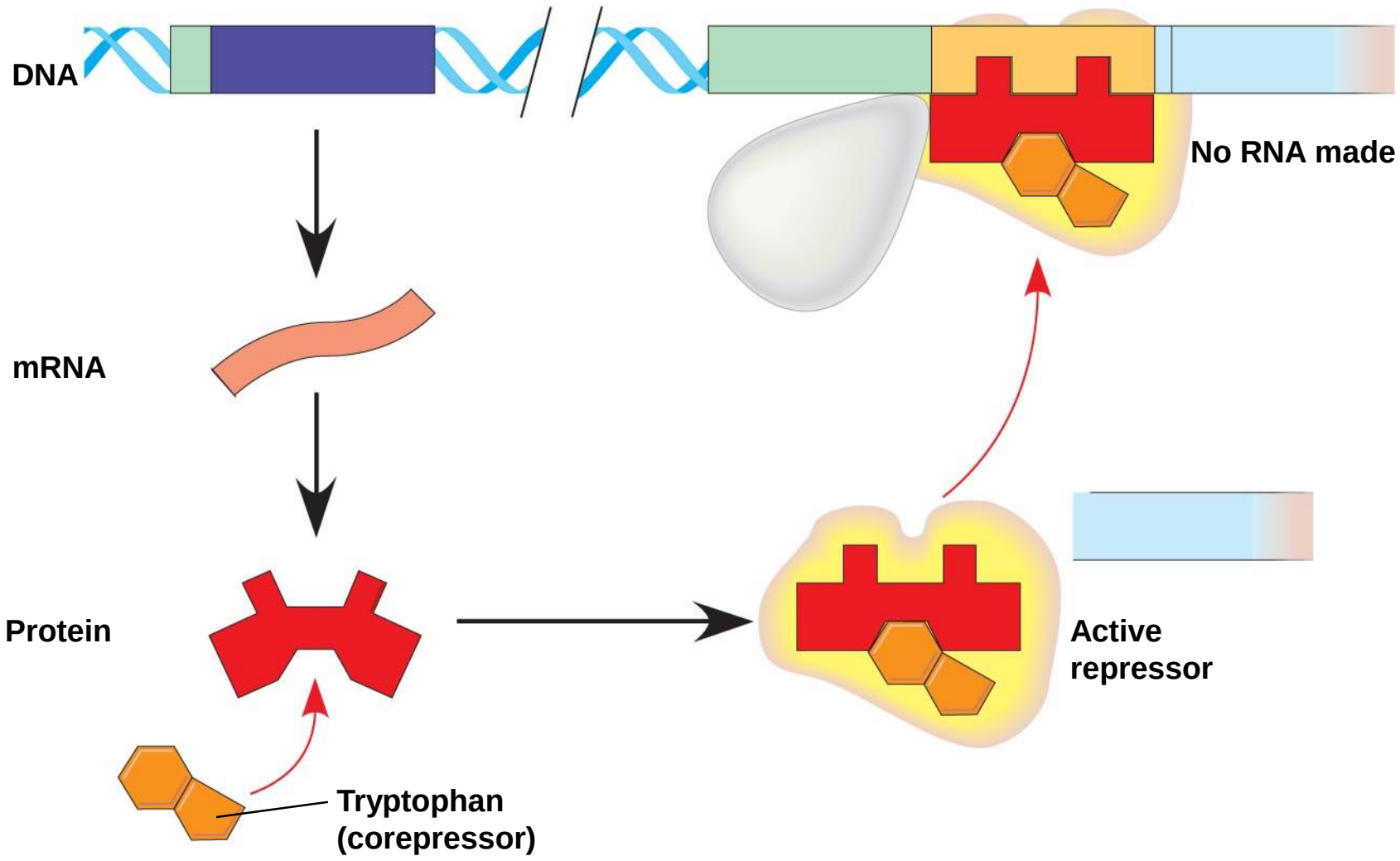



(a) Tryptophan absent, repressor inactive, operon on



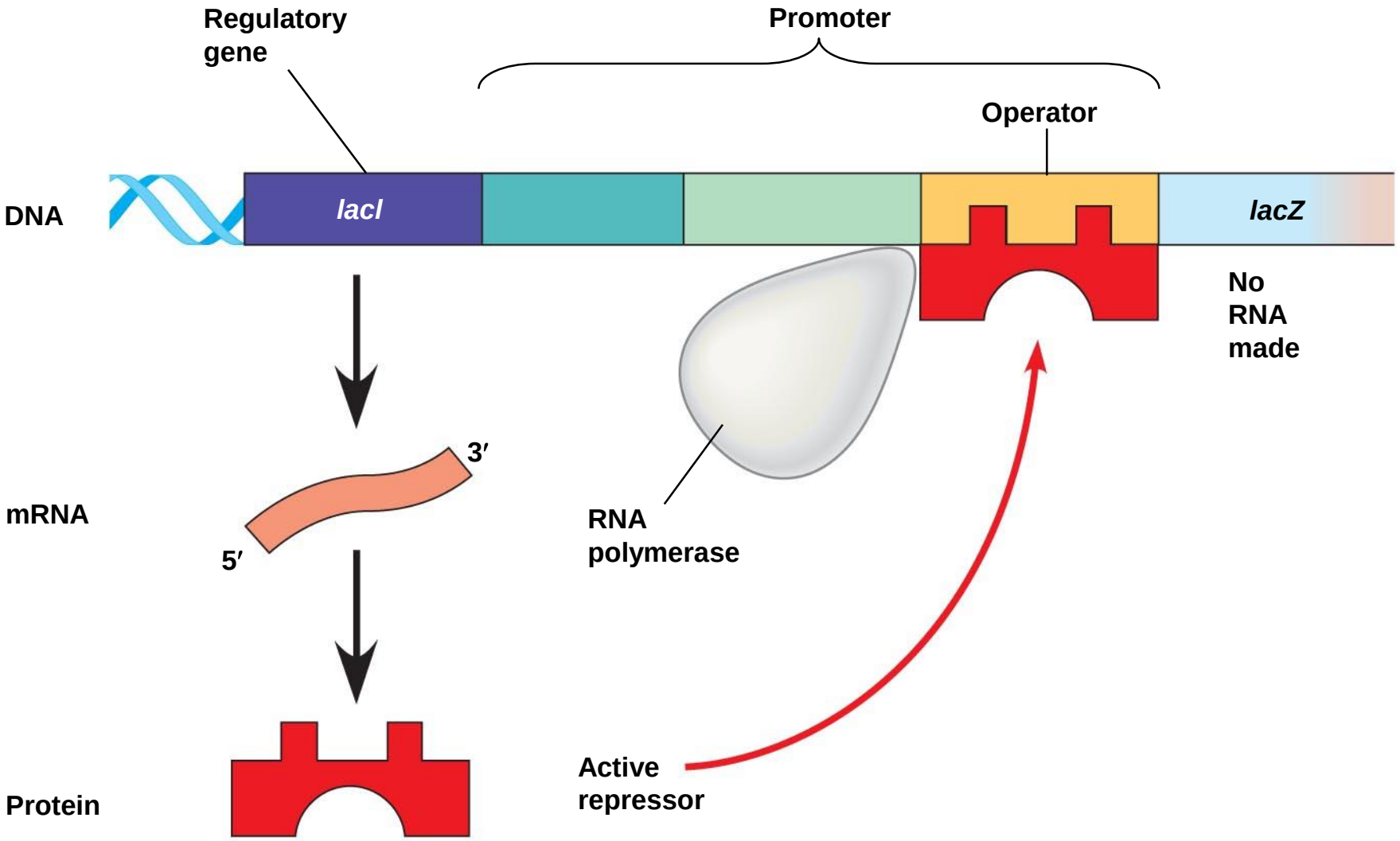

**(b) Tryptophan present, repressor active, operon off**



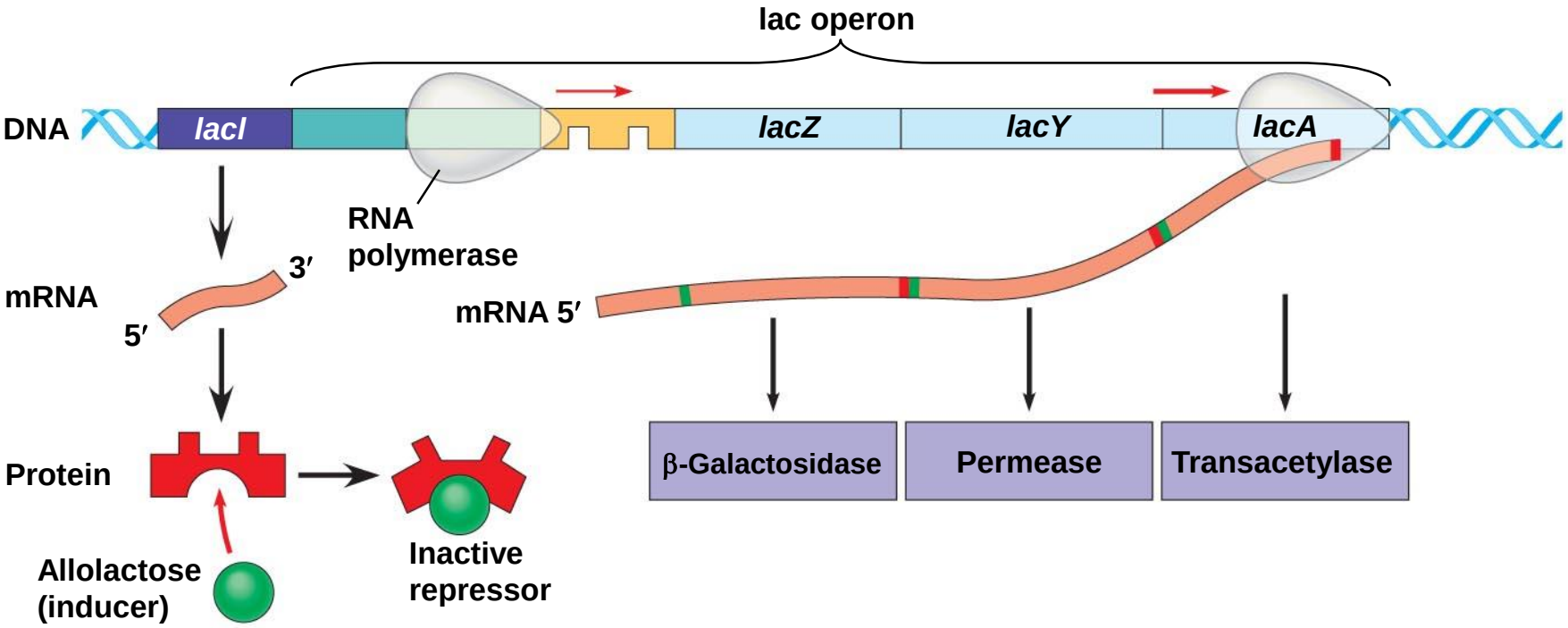

**(b) Tryptophan present, repressor active, operon off**

# Repressible and Inducible Operons: Two Types of Negative Gene Regulation

- A **repressible operon** is one that is **usually on**; binding of a **REPRESSOR** to the operator shuts off transcription
- The ***trp* operon** is a repressible operon
- An **inducible operon** is one that is **usually off**; a molecule called an **INDUCER** inactivates the repressor and turns on transcription
- The classic example of an inducible operon is the ***lac* operon**, which contains genes coding for enzymes used in hydrolysis and metabolism of lactose (disaccharide; “milk sugar”)




(a) Lactose absent, repressor active, operon off

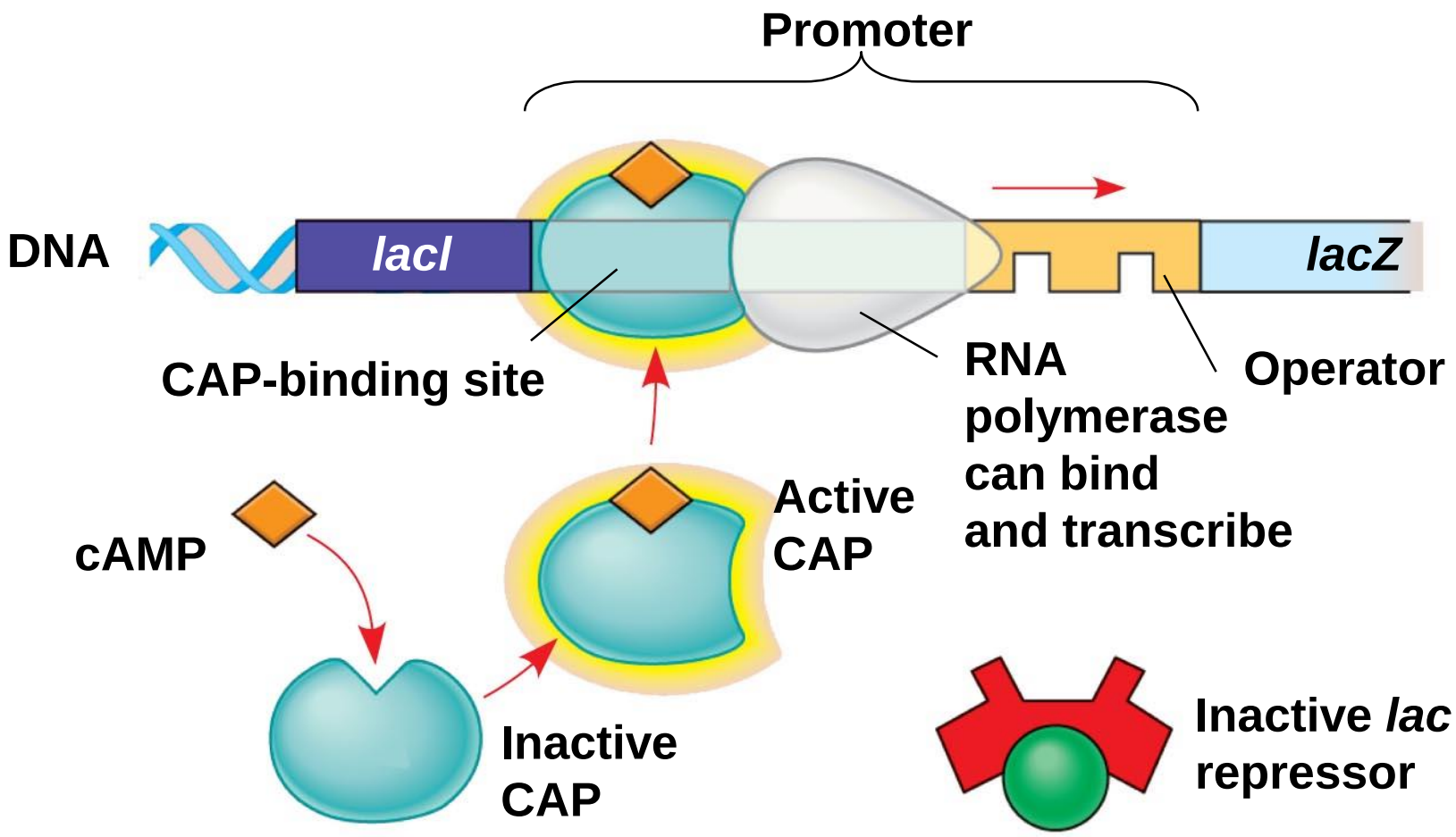



**(b) Lactose present, repressor inactive, operon on**

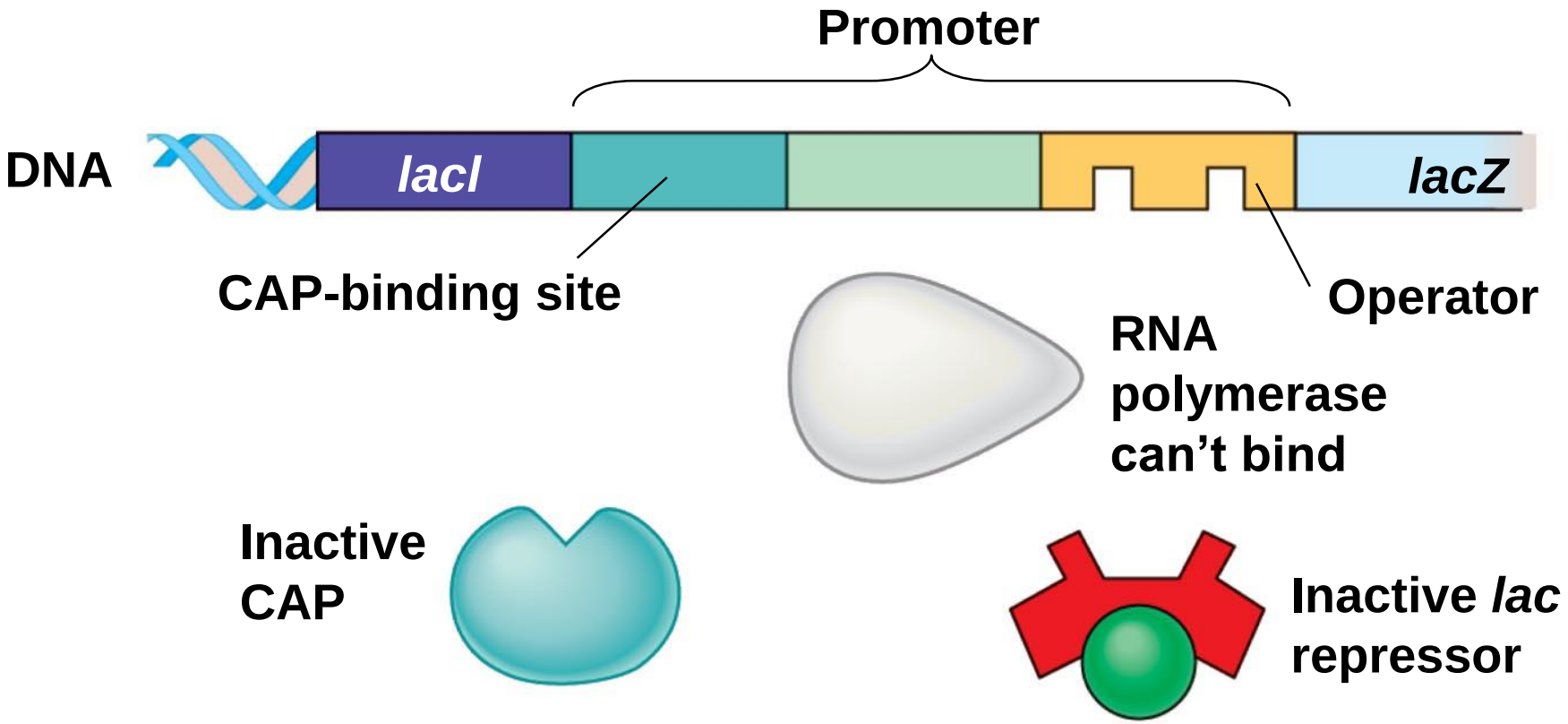
- Inducible enzymes usually function in **catabolic pathways**
- Repressible enzymes usually function in **anabolic pathways**
- Regulation of **both** the *trp* and *lac* operons involves ***negative*** control of genes because operons are switched off by the active form of the repressor

# Positive Gene Regulation

- Some operons are also subject to *positive* control through a stimulatory activator protein, such as **catabolite activator protein** (CAP)
- When glucose (a preferred food source of *E. coli* ) is scarce, the ***lac* operon** is activated by the binding of CAP (so the enzymes to break down lactose are produced)
- When glucose levels increase, CAP detaches from the ***lac* operon**, turning it off

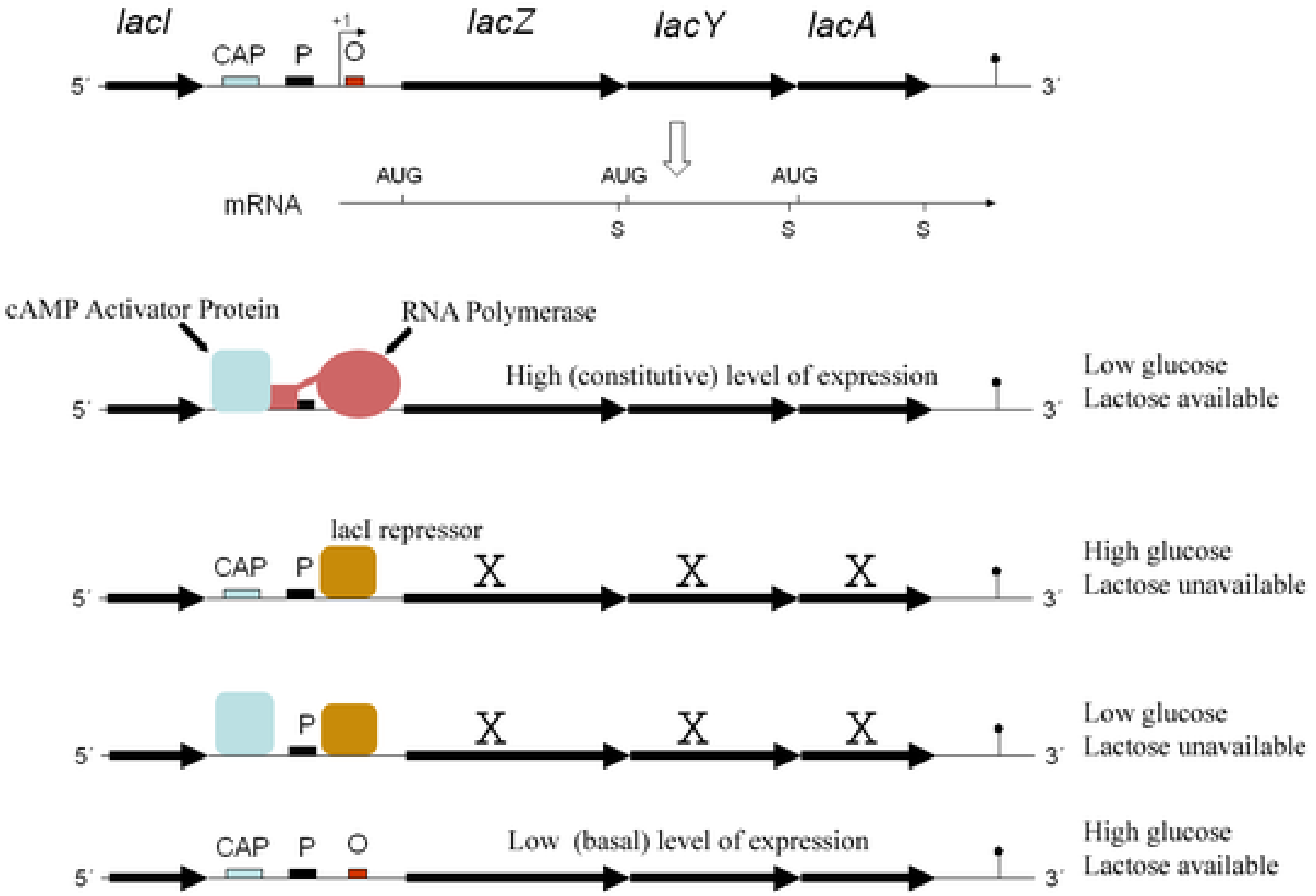



(a) Lactose present, glucose scarce (cAMP level high): abundant *lac* mRNA synthesized




**(b) Lactose present, glucose present (cAMP level low): little *lac* mRNA synthesized**

# The *lac* Operon and its Control Elements



# 18.2: Eukaryotic Gene Expression

- a typical human cell might express about 20% of its protein-coding genes at any given time;
- **specialized cells** (muscle, nerve cells) express an even smaller fraction;
- almost all cells contain an identical genome…however, the subset of genes expressed in each cell type is unique…

- ***DIFFERENTIAL GENE EXPRESSION!***

# 18.2: Eukaryotic Gene Expression

- when gene expression proceeds abnormally, serious imbalances and diseases, **including cancer**, can arise
- as in prokaryotes, much of the regulation of gene expression in eukaryotes occurs at the **transcription stage**…
- however, the greater complexity of eukaryotic cell structure & function provides opportunities for regulating gene expression at many additional stages **(see fig. 18.6)**

# 18.2: Eukaryotic Gene Expression

- eukaryotic gene expression is regulated at many stages:

  **1) regulation of chromatin structure**

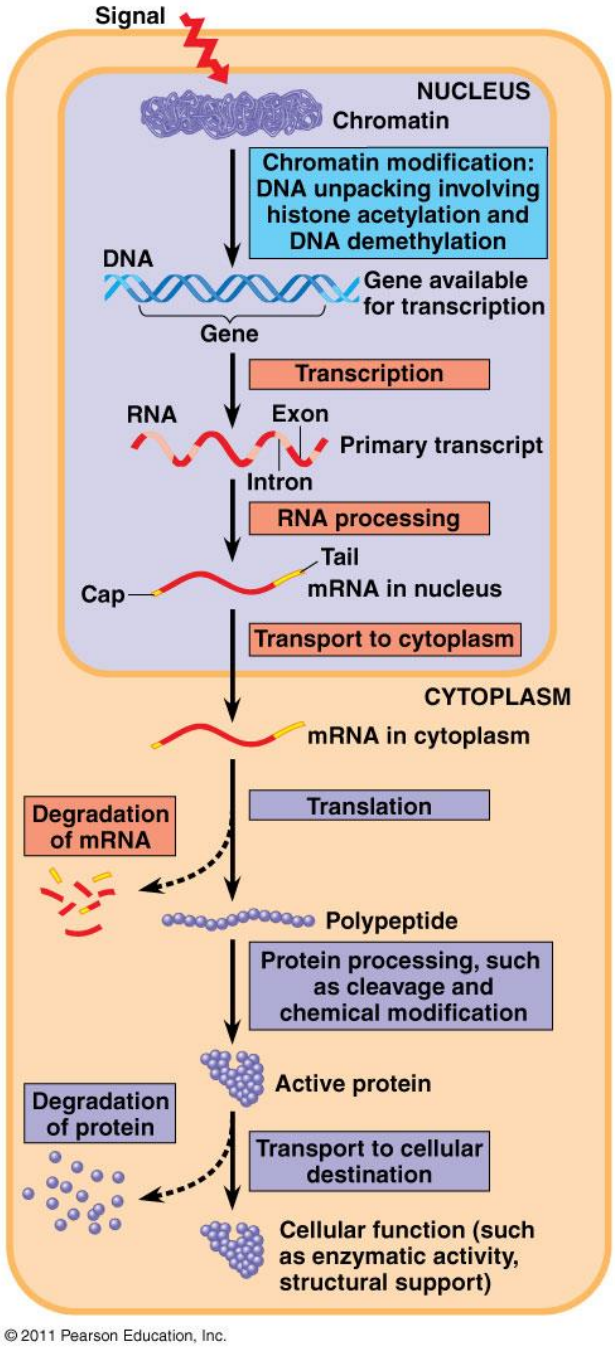
  **2) regulation of transcription initiation**

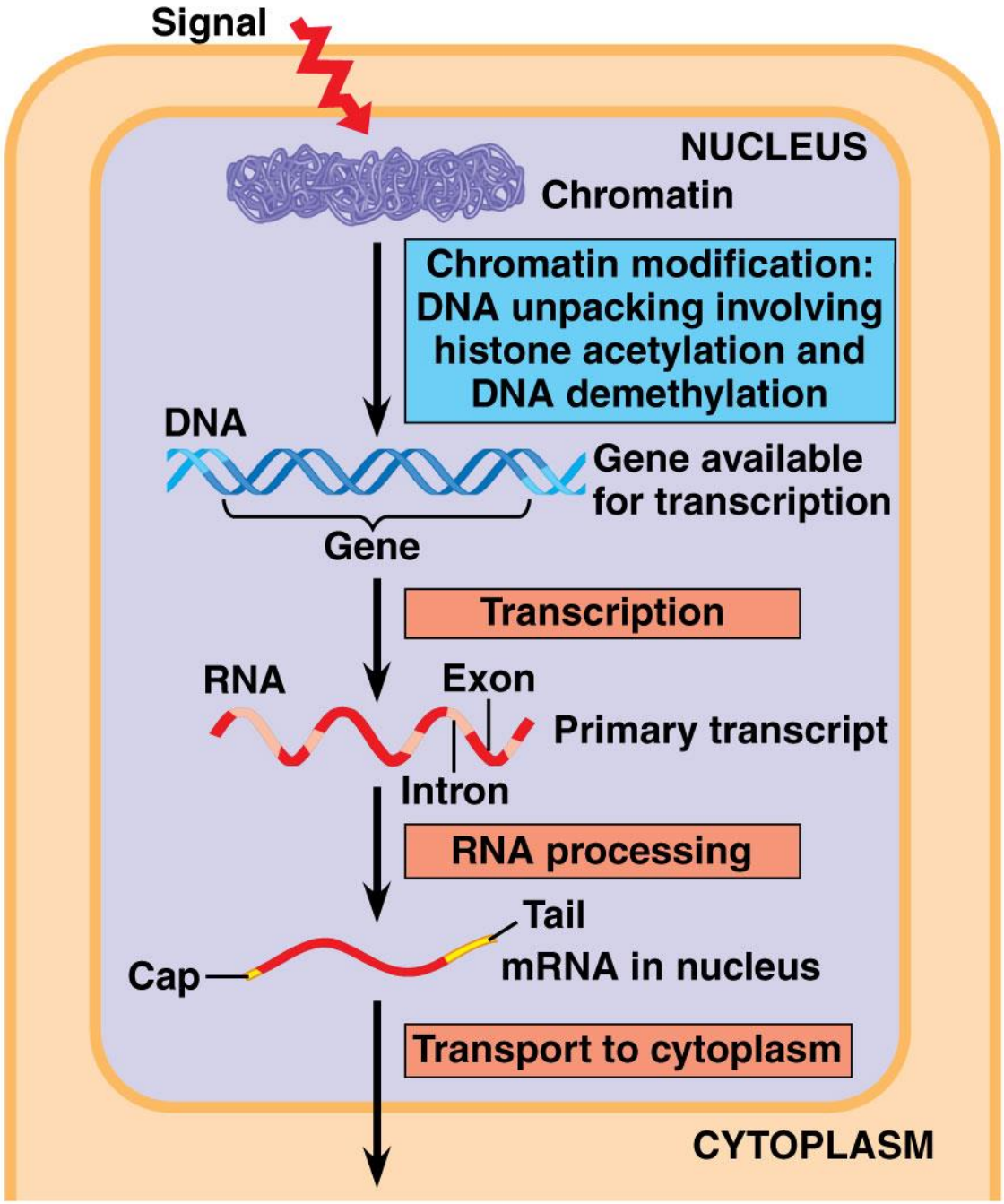
  **3) post-transcriptional regulation**

1) regulation of chromatin structure

2) regulation of transcription initiation

3) post-transcriptional regulation





# 1) regulation of chromatin structure

- recall that the DNA in eukaryotic cells is packaged with proteins (**HISTONES**) into an elaborate complex known as **CHROMATIN**

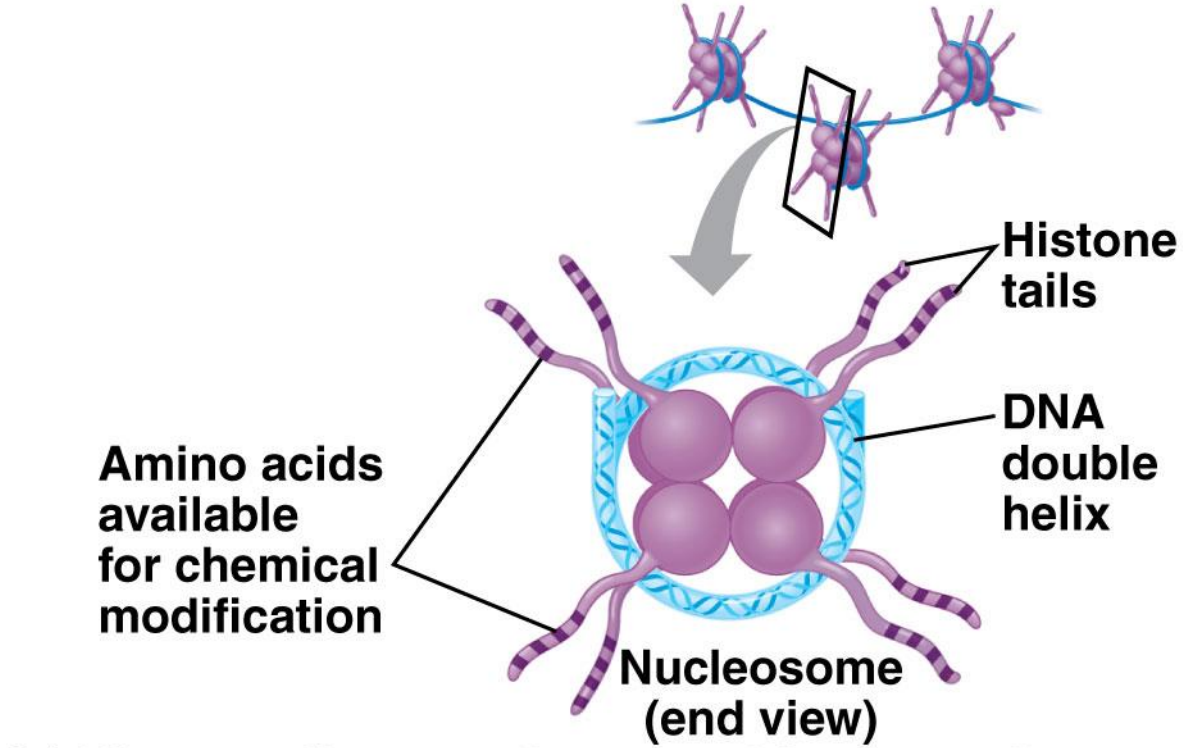
- ***HOW the DNA is packed / coiled regulates how it genes are expressed!***

# 1) regulation of chromatin structure

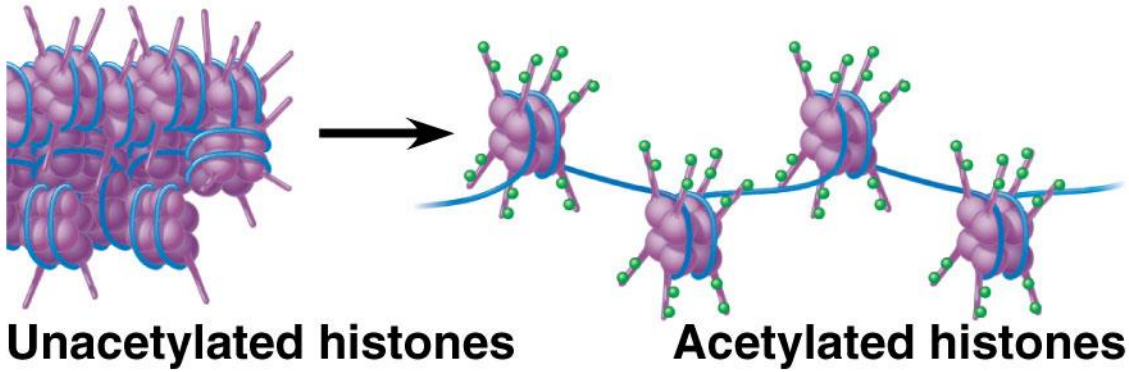
- examples of chromatin modifications:

**A)** **Histone Modifications**: chemical groups (i.e. acetyl groups, methyl groups) can be added to amino acids in the histone structure to alter chromatin folding:

-make the chromatin fold “tighter” (**harder to transcribe**) or “looser” (**easier to transcribe**)




(a) Histone tails protrude outward from a nucleosome




(b) Acetylation of histone tails promotes loose chromatin structure that permits transcription

# 1) regulation of chromatin structure

- examples of chromatin modifications:

**B)** **<u>DNA Methylation</u>**: enzymes add methyl groups ($CH_3$) to certain bases in DNA (usually cytosine)…typically <u>inactivates these segments of DNA</u>

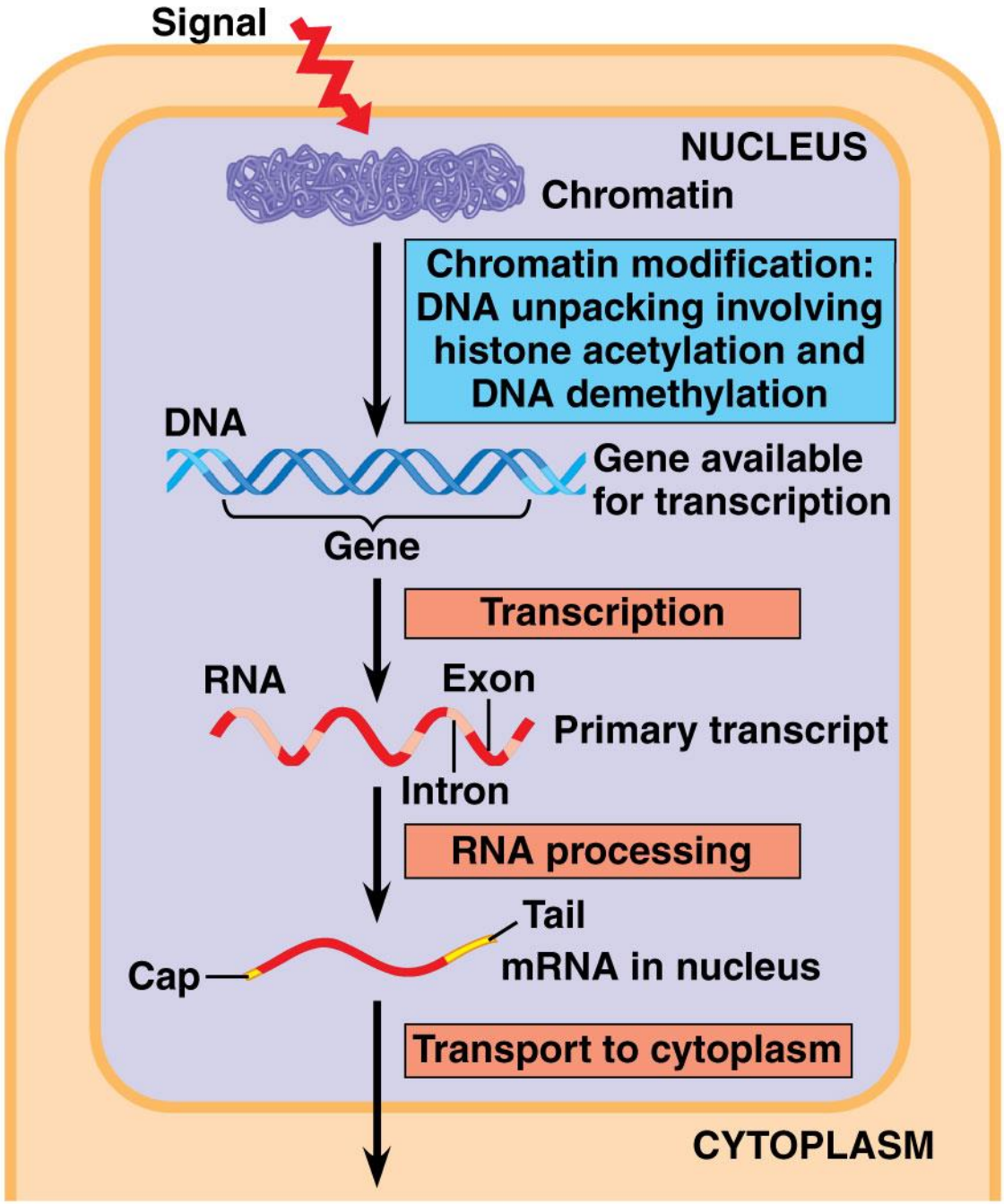
-**evidence**: individual genes are more heavily methylated in cells **<u>in which they are NOT expressed</u>**…removal of these methyl groups can turn some of these genes on!

# 1) regulation of chromatin structure

- examples of chromatin modifications:

**C) <u>Epigenetic Inheritance</u>**: inheritance of traits transmitted by <u>mechanisms not directly involved with the DNA nucleotide sequence</u> (i.e. histone modifications & DNA methylation!)…

-these are modifications that can typically be reversed!

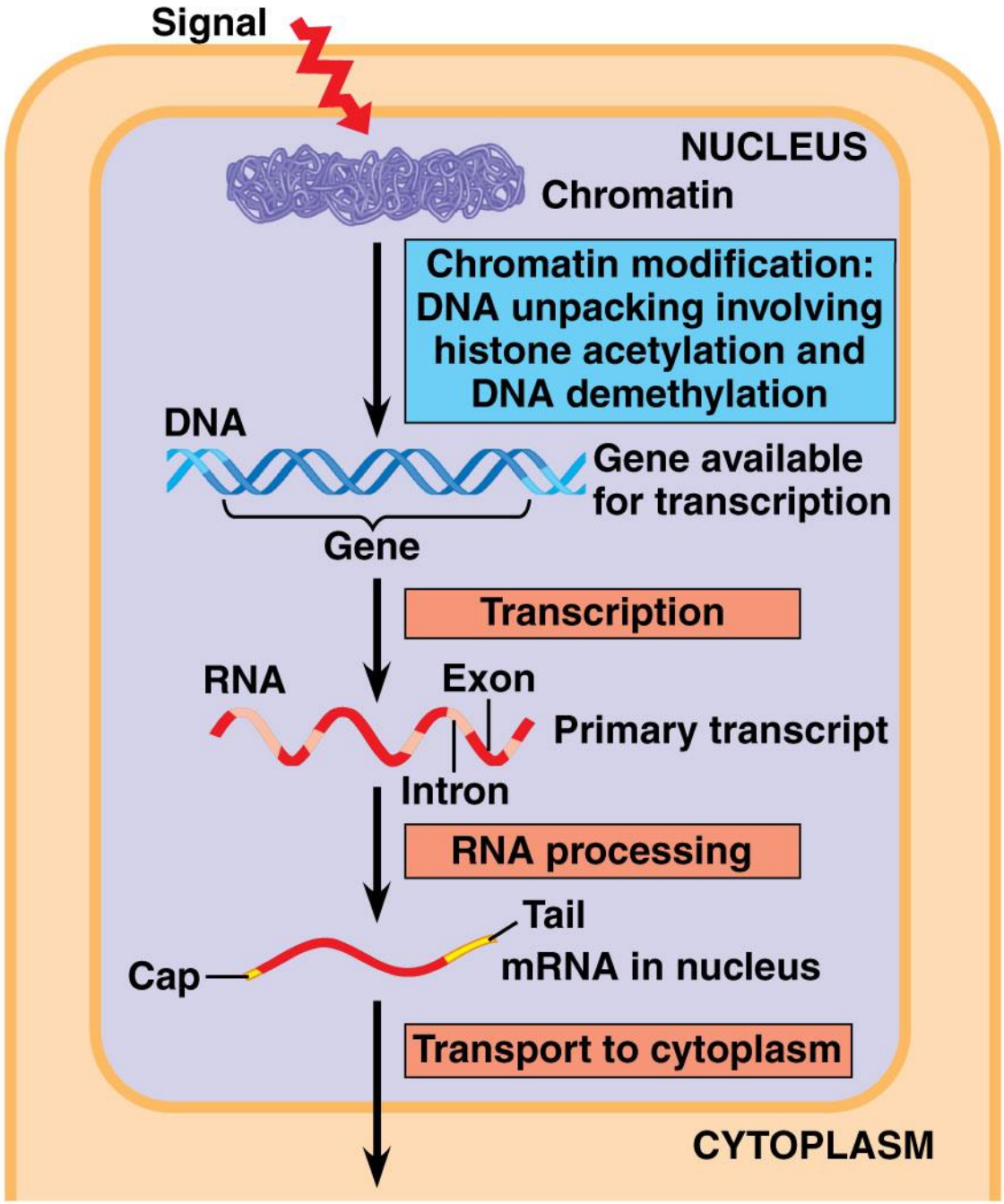


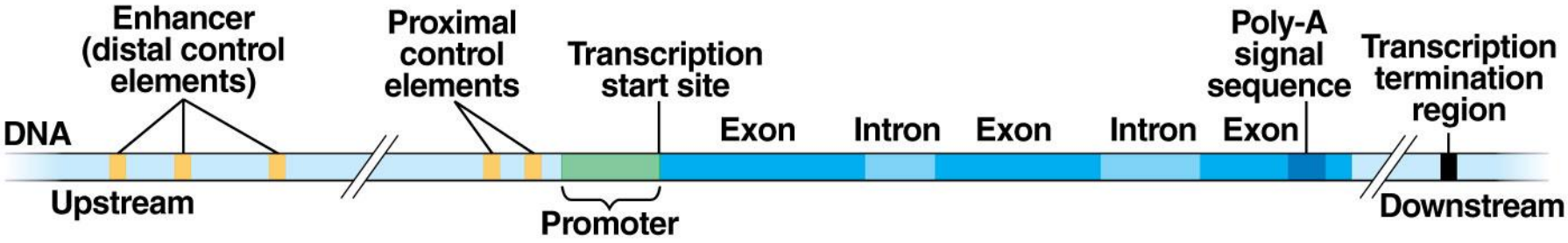
# 2) regulation of transcription initiation

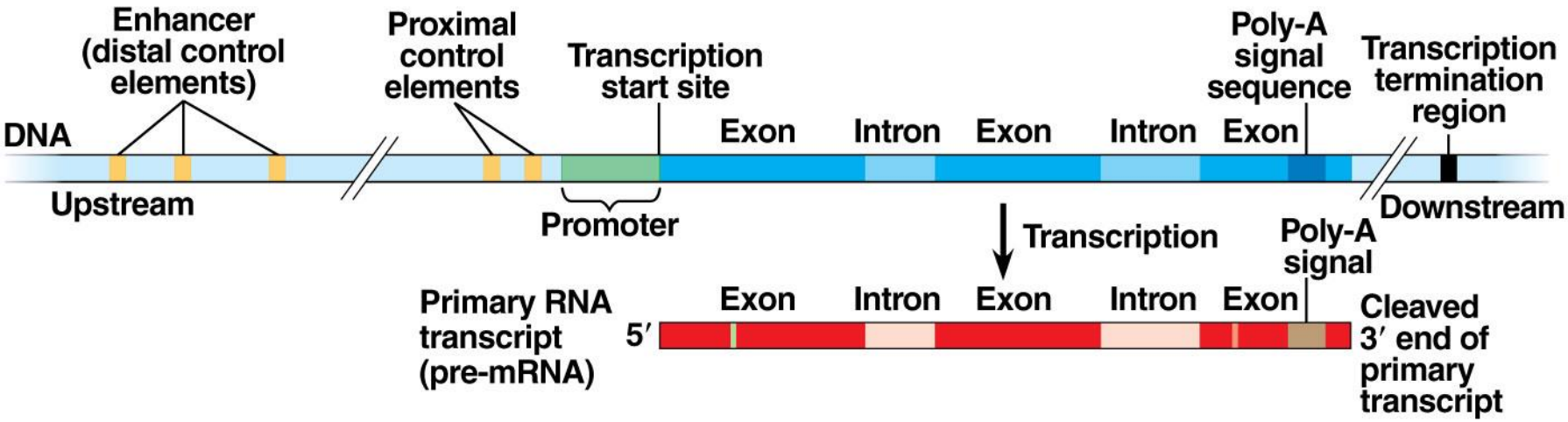
- most eukaryotic genes have multiple **control elements** – segments of noncoding DNA that serve as binding sites for proteins known as **TRANSCRIPTION FACTORS,** which in turn regulate transcription

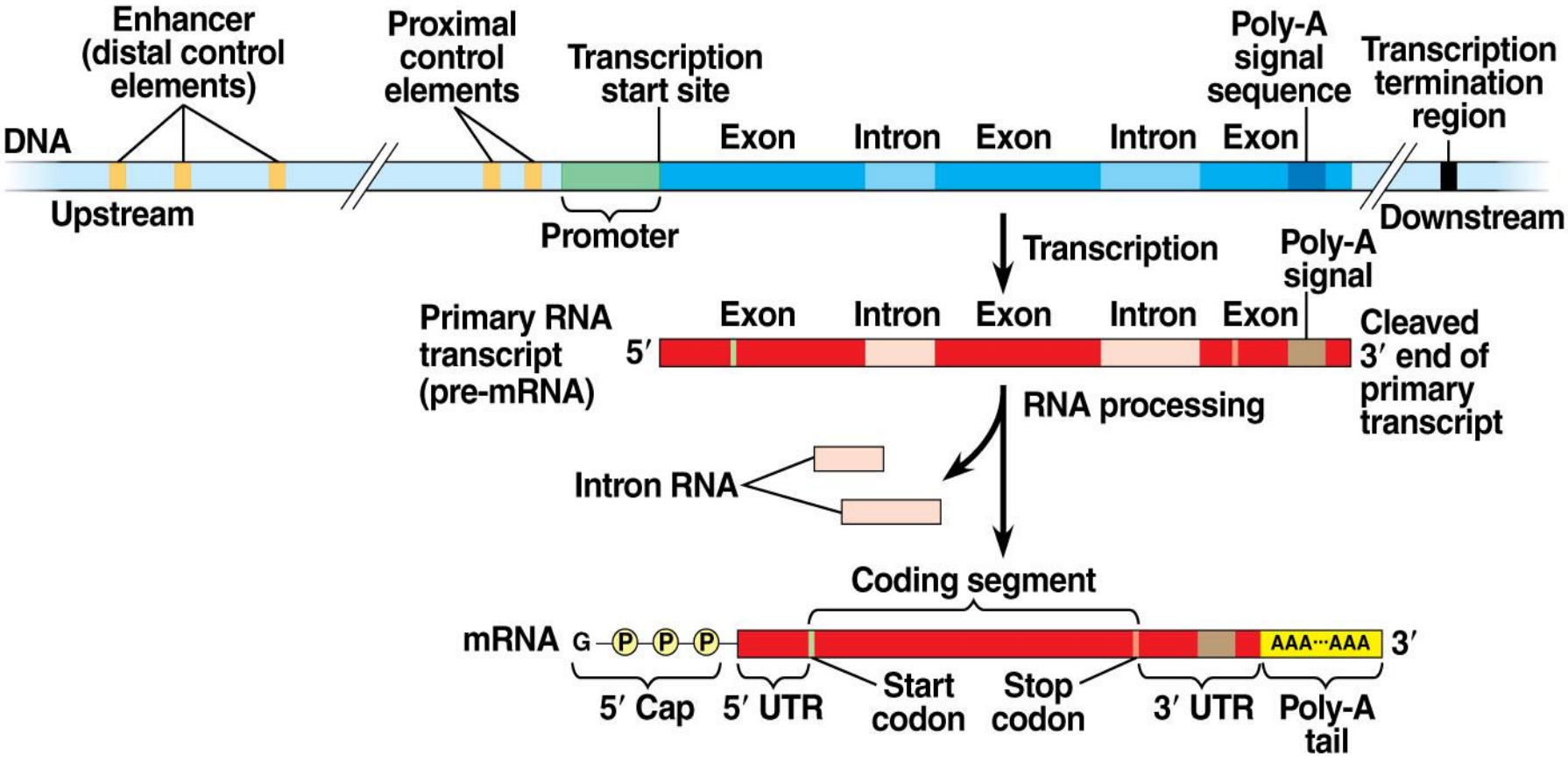
# 2) regulation of transcription initiation

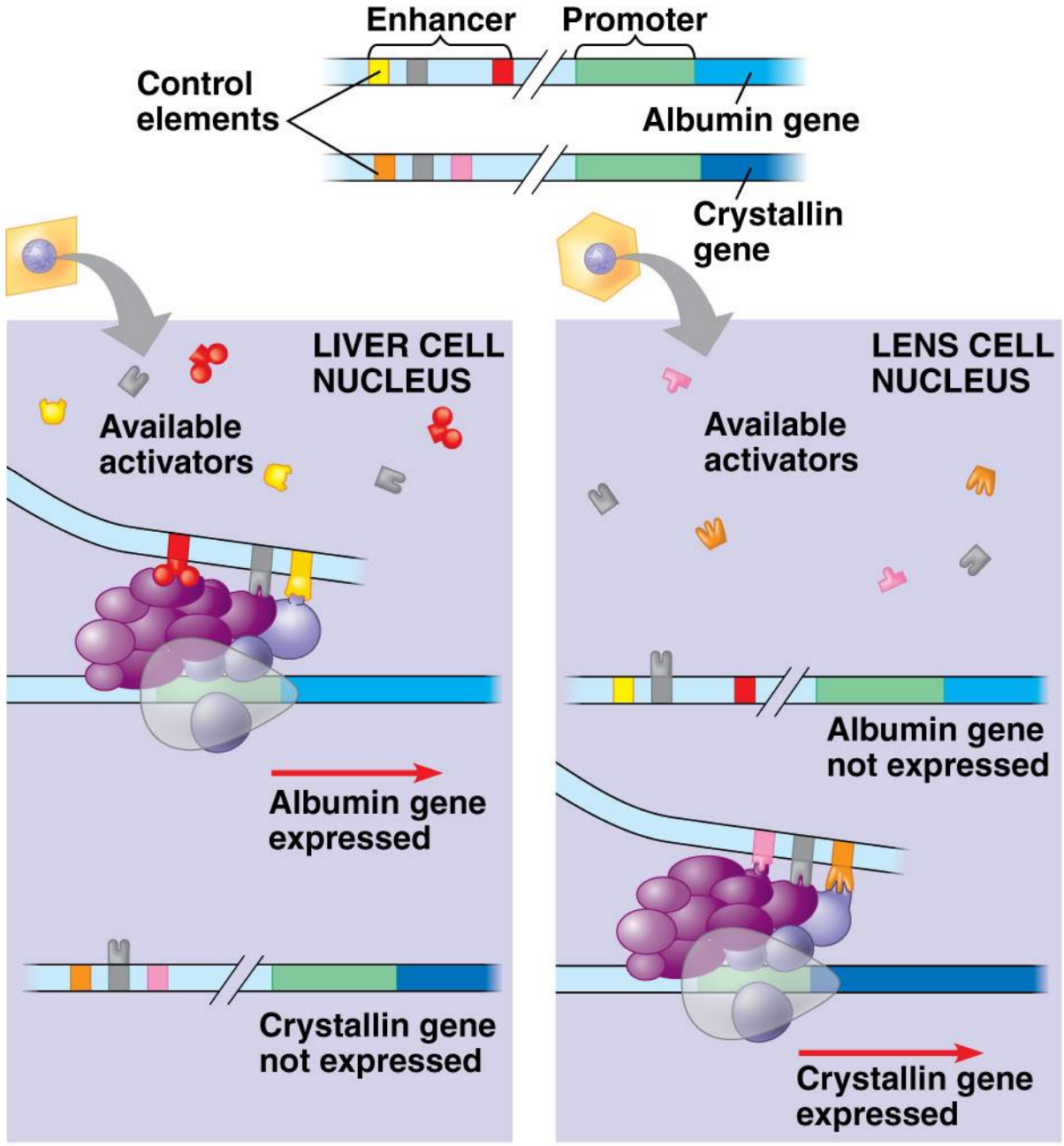
- as we saw in CH 11 (Cell Signaling), **signaling molecules (i.e. steroid or non-steroid hormones)** can cause the activation of one or more transcription factors, turning “on” the transcription of one or more genes












(a) Liver cell

(b) Lens cell

# 3) post-transcriptional regulation

- transcription alone does not constitute gene expression…the expression of a protein-coding gene is ultimately measured by **the amount of functional protein it makes**!

# 3) post-transcriptional regulation

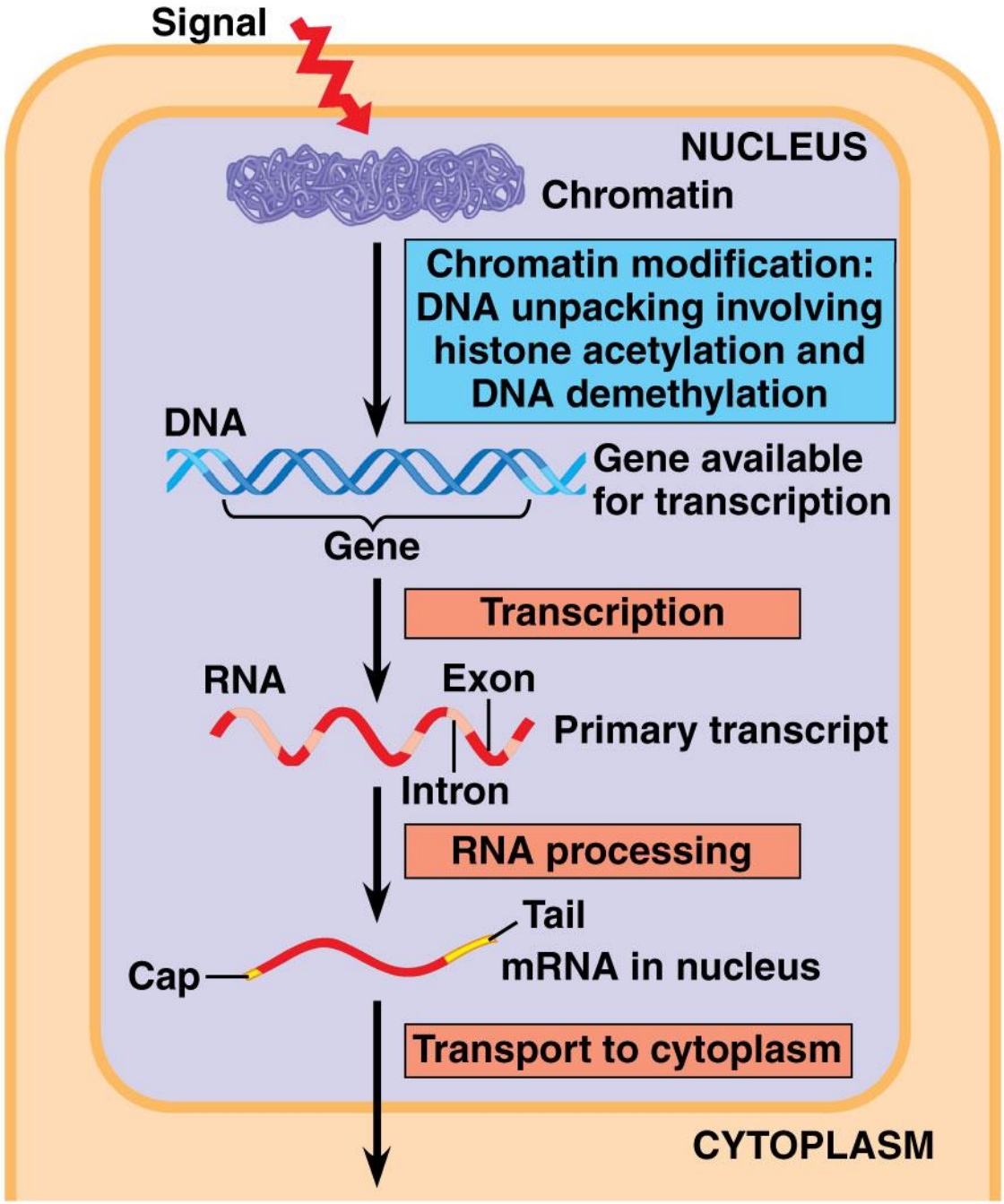
- much happens between the synthesis of mRNA and the activity of the protein in the cell:

**A) RNA Processing**

**B) mRNA Degradation**

**C) Initiation of Translation**

**D) Protein Processing and Degradation**



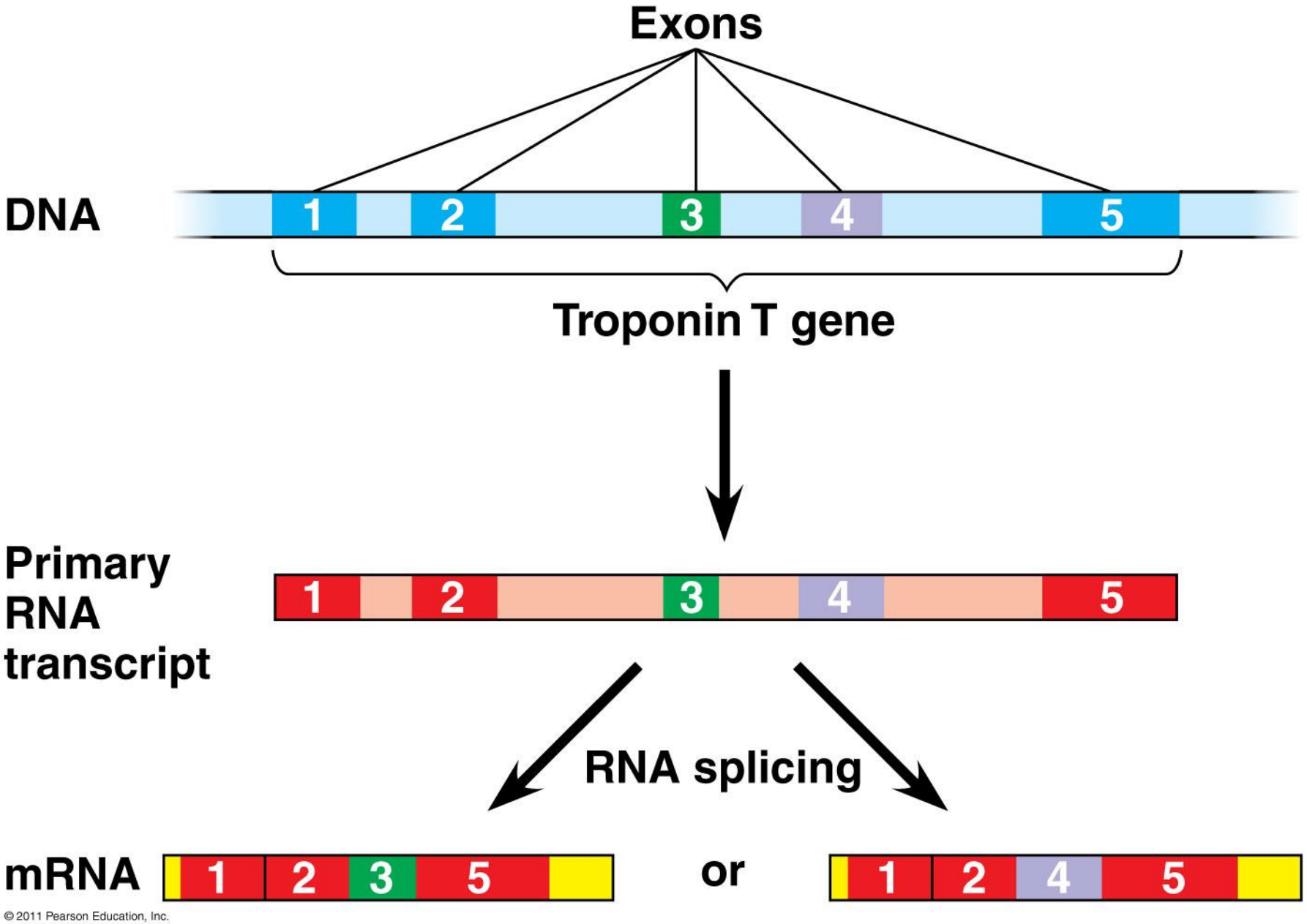
# A) RNA Processing

- we've already discussed: 5' cap, 3' poly-A tail, and removal of introns (**exons remain**)

# A) RNA Processing

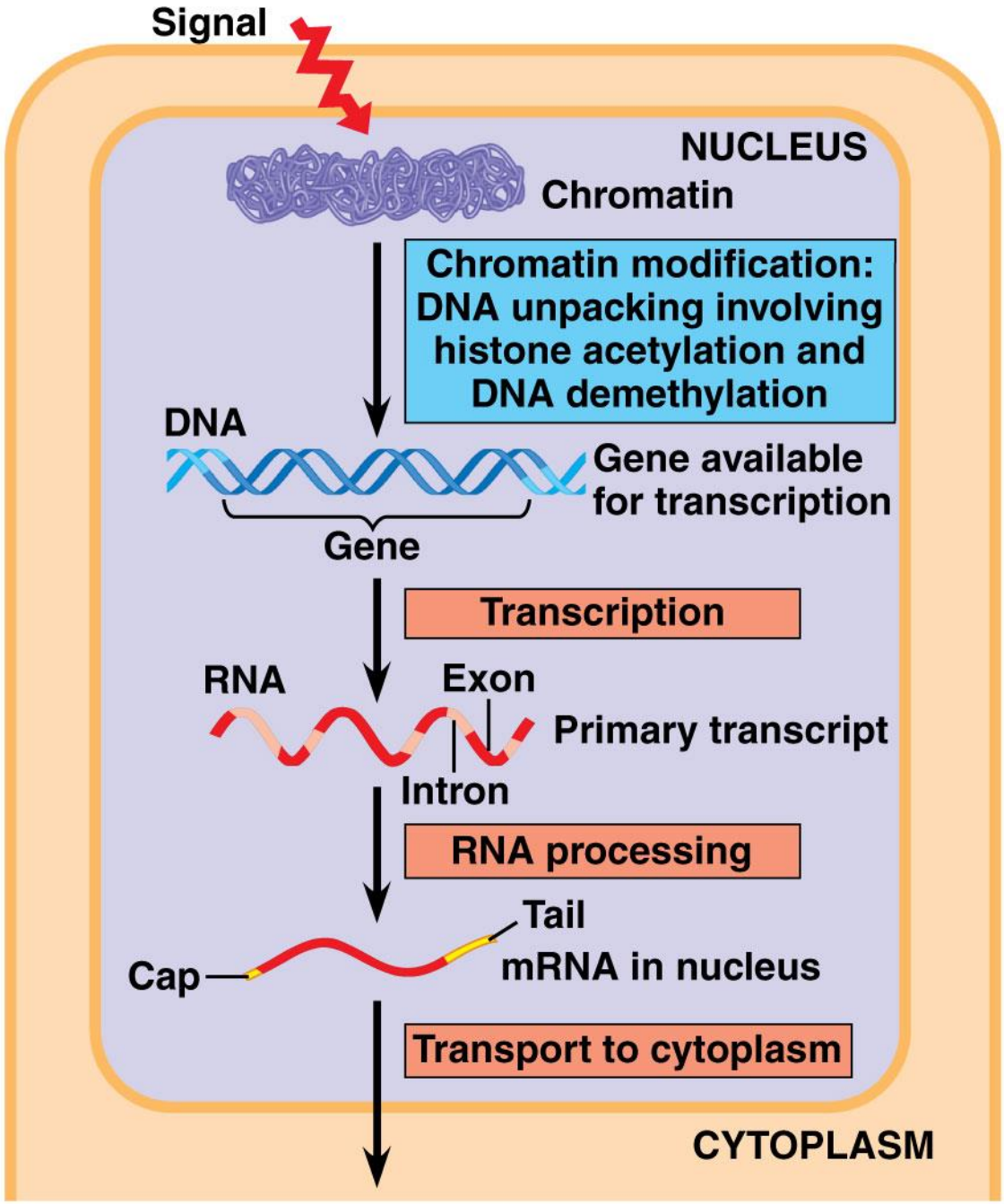
- **alternative RNA splicing**: different mRNA molecules can be made from the same primary transcript! (depending on which RNA segments are treated as exons & which as introns)

-**example**: researchers have found 1 Drosophila gene with enough alternatively spliced exons to produce **19,000 membrane proteins** that have different extracellular domains!!!



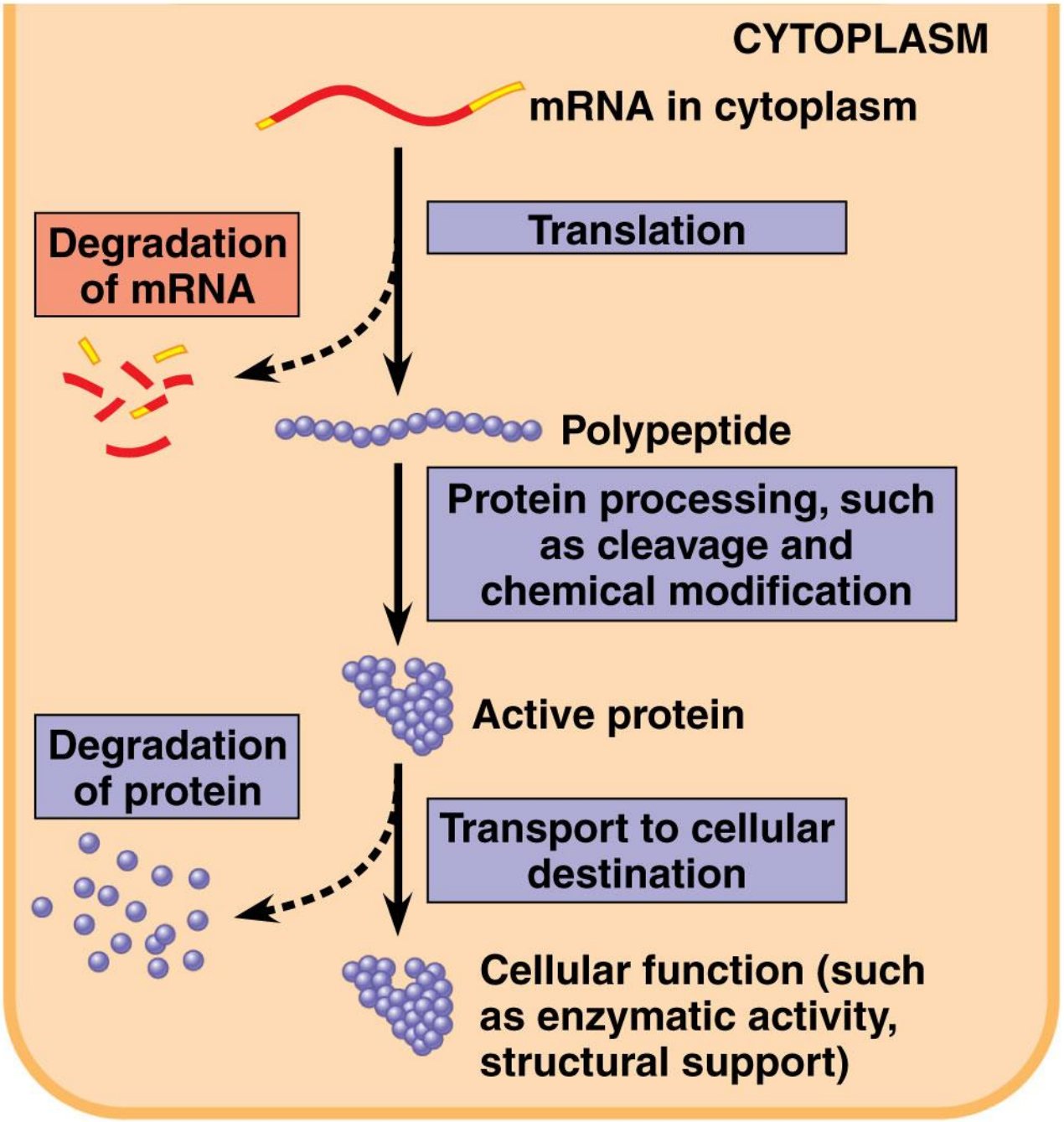
# B) mRNA Degradation

- the lifespan of mRNA molecules in the cytoplasm is important in determining the pattern of protein synthesis
- **bacterial mRNA** molecules are typically degraded by enzymes within a few minutes
- **eukaryotic mRNAs** are typically more stable…can last for hours, days, weeks… ***(i.e. mRNAs for hemoglobin polypeptides are long-lived!)***



# C) Initiation of Translation

- there are regulatory proteins that can bind to specific sequences at the 5’ or 3’ end of mRNA & prevent the attachment of ribosomes



# D) Protein Processing and Degradation

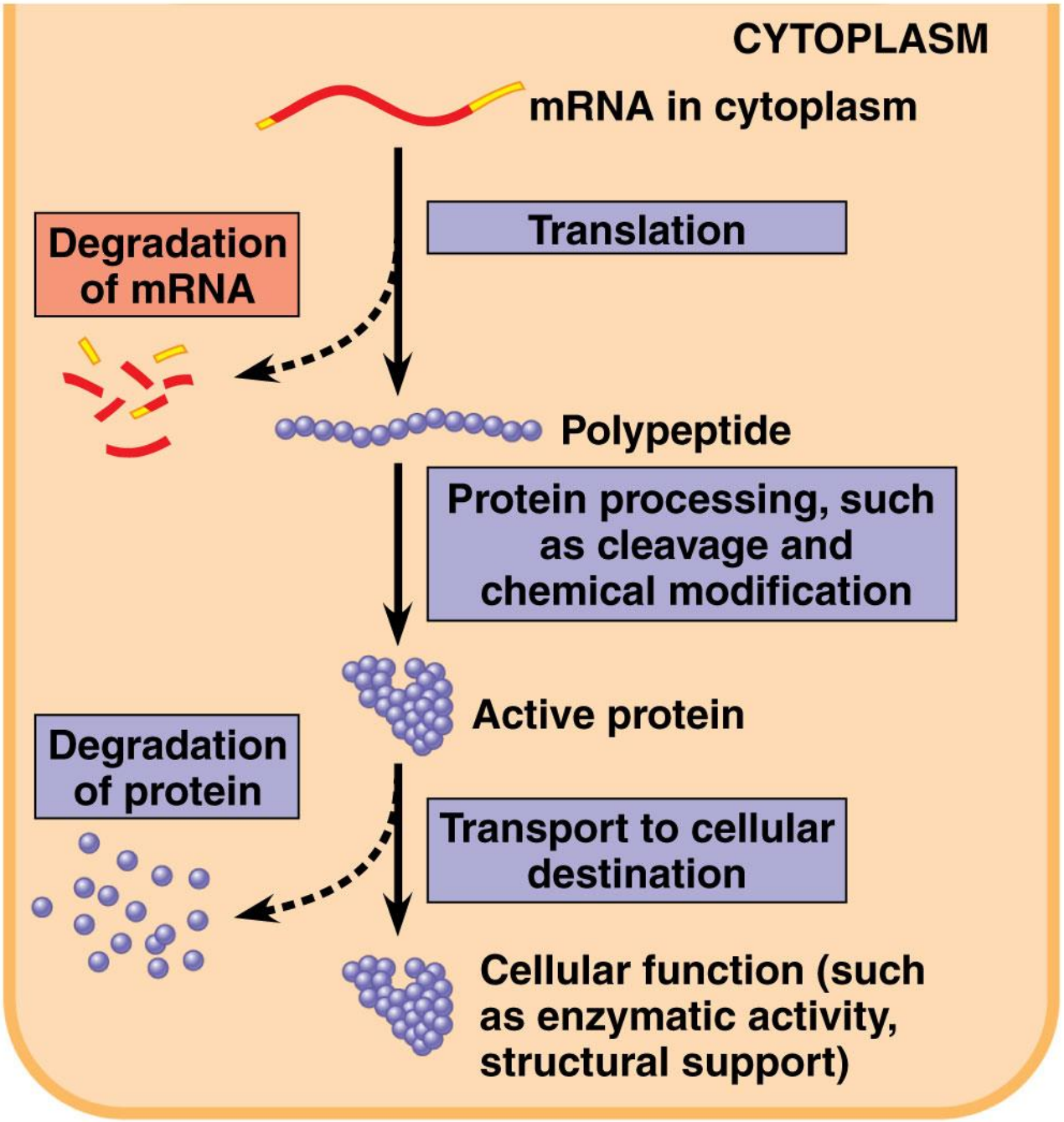
- most polypeptides require some processing before they are functional

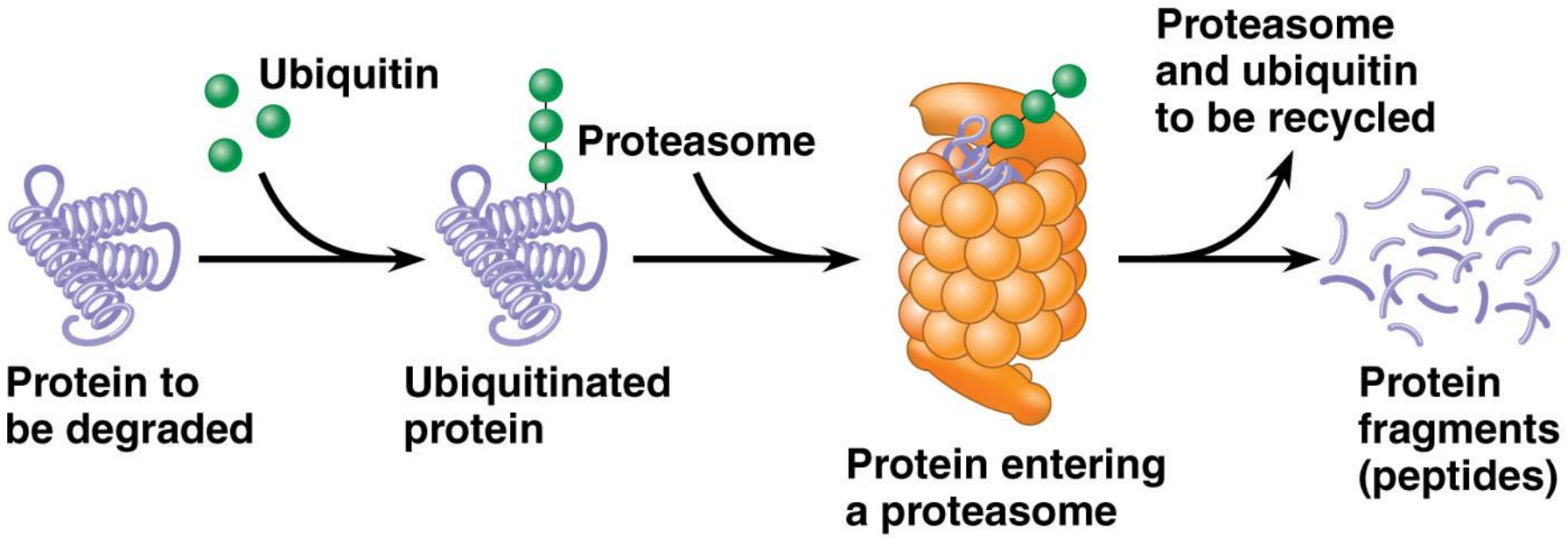
  -phosphate groups added / removed

  -transported to target destination (i.e. cell surface)

  -proper folding or combining with other polypeptides to form quaternary structure…

***regulation can occur at any of these steps!**





# 18.3: Noncoding RNAs play multiple roles in controlling gene expression

- genome sequencing has shown that protein-coding DNA only accounts for 1.5% of the human genome (& other eukaryotes)
- a small fraction of the non-protein coding DNA consists of genes for rRNAs and tRNAs

# 18.3: Noncoding RNAs play multiple roles in controlling gene expression

- until recently, researchers assumed that most of the remaining DNA was untranscribed…"junk" DNA
- however, new research suggests that a significant amount of the genome may be transcribed into non-protein-coding RNAs that are involved in regulation of gene expression!!

  -**noncoding RNAs** (ncRNAs)

  -**microRNAs** (miRNAs)

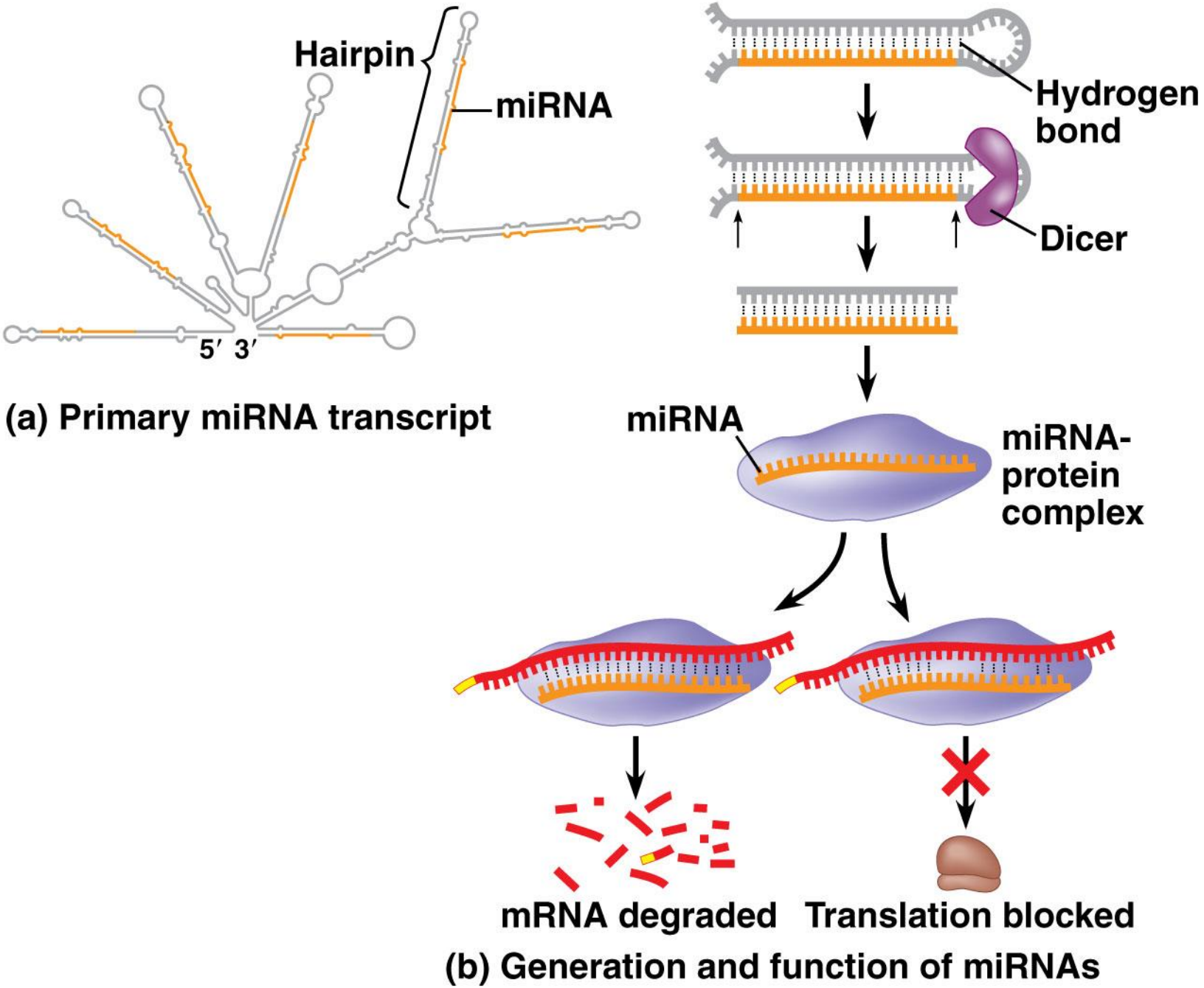
  -**RNA interference** (RNAi)

  -**small interfering RNAs** (siRNAs)

# microRNAs (miRNAs)

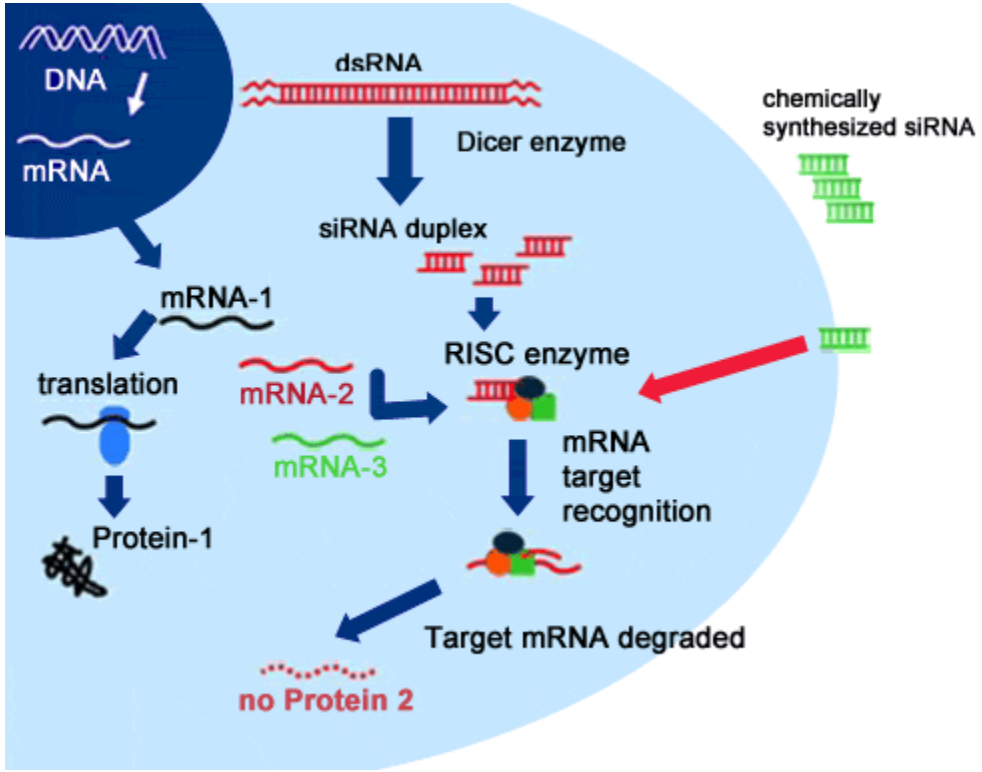
- small, single-stranded RNA molecules
- capable of binding to complementary sequences in mRNA

- typically, a miRNA forms a complex with 1 or more proteins; this complex then binds with a mRNA
- the result is the mRNA is either degraded or translation of it is blocked



# RNA interference (RNAi)

- **small interfering RNAs (siRNAs)**, similar to miRNAs, can associate with the same proteins as miRNAs and block expression of a gene with the same sequence as the RNA…



**LINK to RNA interference video!**