Controlling Gene Expression

Figure 5 A mouse whose agouti genes have been turned on (left) is very different from a mouse whose agouti genes have been silenced.

Control Mechanisms

- **Gene regulation** involves turning on or off specific genes as required by the cell
- Determine when to make more proteins and when to stop making more
- ***Housekeeping genes*** are always needed and are constantly being transcribed and translated. These genes are always turned on

Control Mechanisms in Eukaryotes

- **Transcription factors** are proteins that turn on genes by binding to DNA and helping RNA polymerase bind.

There are Four Levels of Control in Eukaryotes:

1) **Transcriptional** (controls transcription from DNA to mRNA)

2) **Posttranscriptional** (controls the removal of introns)

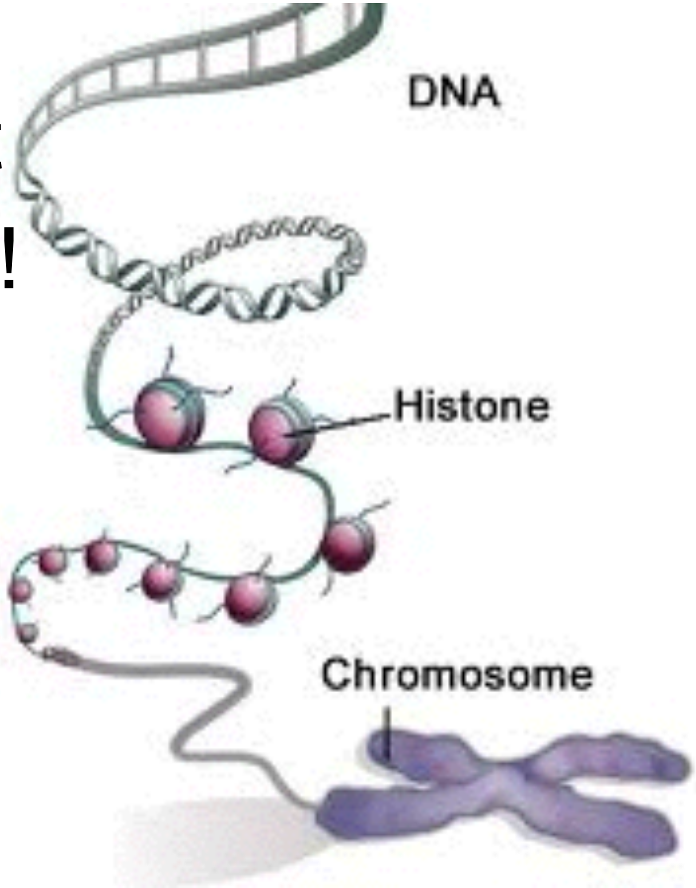
3) **Translational** (controls rate that mRNA is activated through ribosomes)

4) **Posttranslational** (affects the rate proteins can leave the cell)

1) Transcriptional Regulation

- Most common type of regulation
- DNA of Eukaryotes is wrapped tightly around histone proteins
- In this form, genes are not

accessible to be transcribed!



Transcription Activators:

- Activator molecule binds to DNA and helps "loosen" the coils so that the gene is exposed for transcription:
  - i) Signals a protein remodelling complex, displacing core histone proteins and exposing the promoter region of the gene
  - ii) Can also signal an enzyme to add an acetyl (CH_3COO-) group to histone proteins, which loosens their hold with DNA

Transcription Activators:

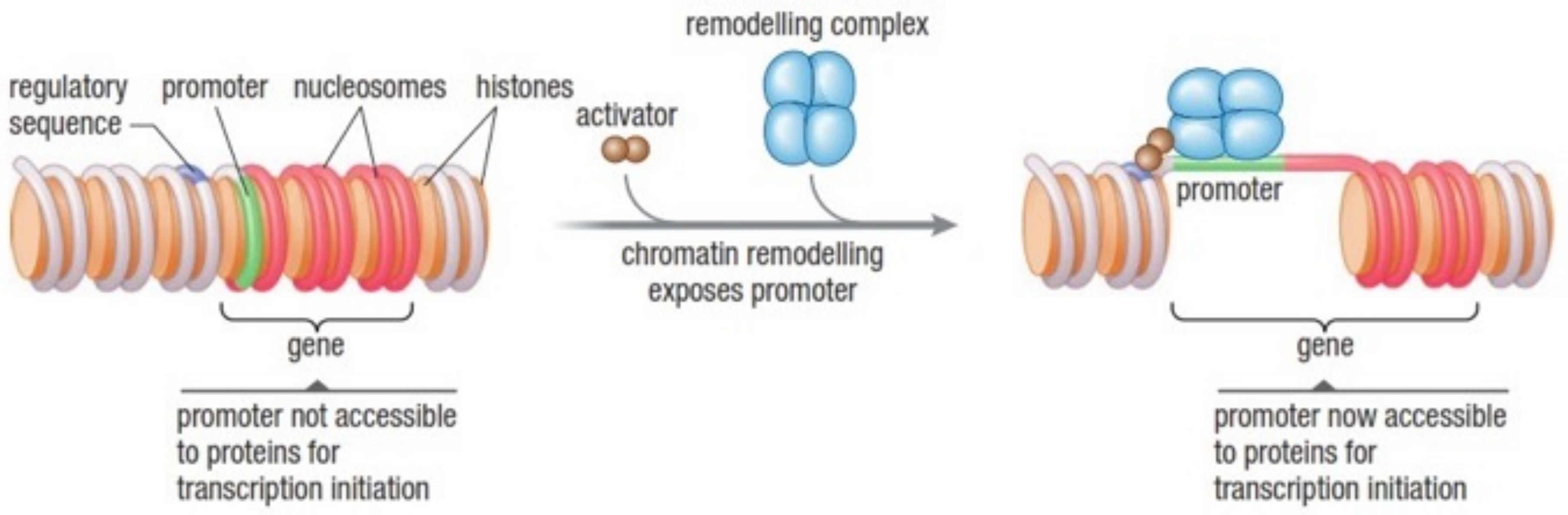
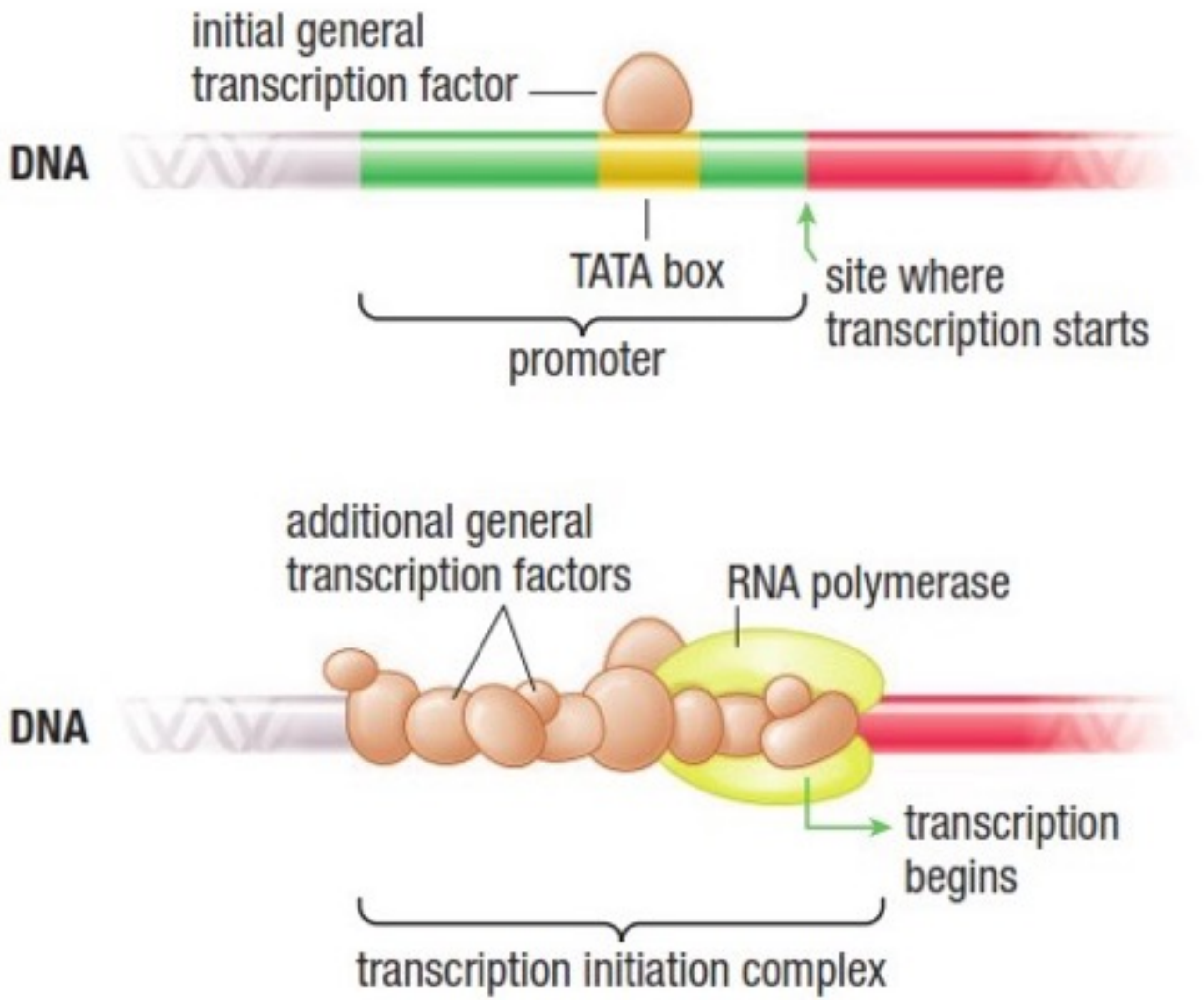


Figure 3 A chromatin remodelling complex exposes the promoter, and thus enables transcription.

General Transcription Factors

- Series of proteins that bind to the promoter region of gene (the TATA box)
- Provides substrate for RNA polymerase to bind to and begin transcription
- Together, form the transcription initation complex

General Transcription Factors



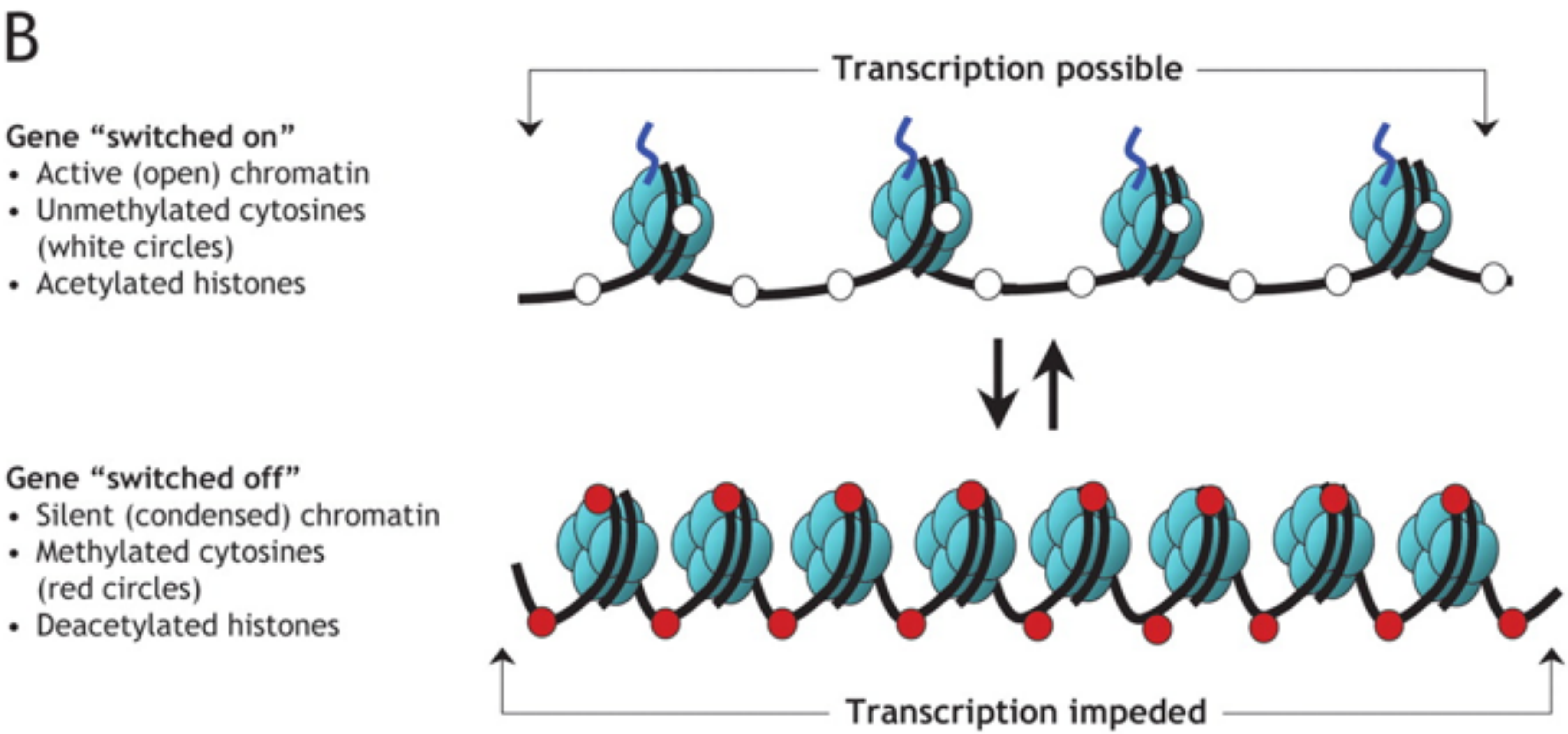
1 The first general transcription factor recognizes and binds to the TATA box of a protein-coding gene's promoter.

2 Additional general transcription factors and then RNA polymerase add to the complex, and then transcription begins.

Transcription Repressors

- Methylation adds a methyl (CH_3) group to promoter region of gene, inhibiting transcription and thus gene expression
- Gene silencing can put entire regions of chromosomes "on hold" unless needed
    - E.g. genes that regulate the production of hemoglobin only need to be active in bone marrow where blood cells are formed, they are silenced everywhere else

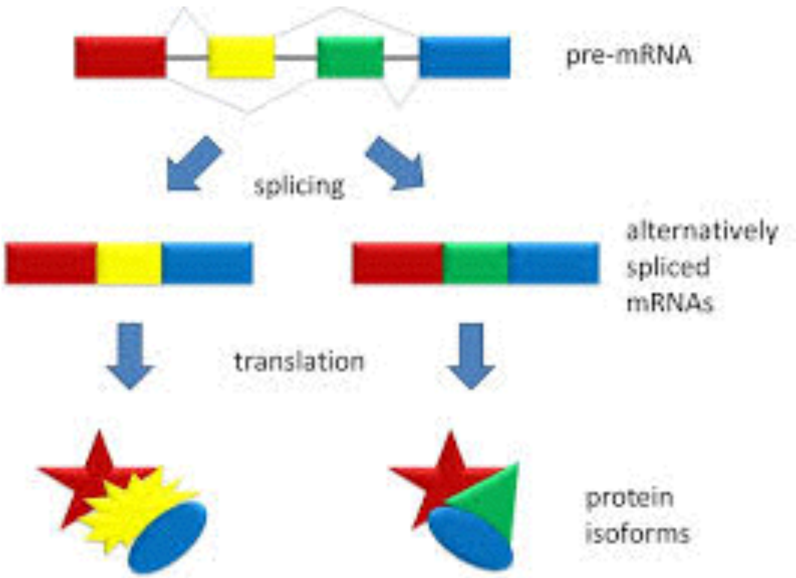
Transcription Activators and Repressors: On-Off Switches of the Genes!



2) Post-Transcriptional Regulation

i) Alternative splicing of pre-mRNA molecule

- Produces different versions of related proteins



- Perhaps 75% of human genes are alternatively spliced

2) Post-Transcriptional Regulation

ii) Masking proteins

- Bind to mRNA and inactivates it, preventing gene translation

iii) Degradation of mRNA

- Regulatory molecules like hormones can affect the rate of mRNA breakdown

3) Translational Regulation

Occurs during protein synthesis by ribosomes

i) Masking proteins

- Can bind to mRNA strand or ribosomes, preventing translation from occurring

ii) Length of poly-A tail

- Can increase or decrease time required to translate the mRNA into a protein

4) Post-Translational Regulation

After protein is formed, the cell can still regulate its function by:

i) Processing
   - Sections of a protein can be removed to render it inert until needed (e.g. proinsulin and insulin)

ii) Modification
   - Chemical groups can be added or deleted to put protein on hold until needed

iii) Degradation
   - Adding or removing protein tags like ubiquitin can mark the protein to be degraded

Four Levels of Eukaryotic Control

Table 1 Four Levels of Control of Gene Expression in Eukaryotic Cells

Type of control	Description
transcriptional	It regulates which genes are transcribed (DNA to mRNA) or controls the rate at which transcription occurs.
posttranscriptional	The mRNA molecules undergo changes in the nucleus before translation occurs. Introns are removed and exons are spliced together.
translational	It controls how often and how rapidly mRNA transcripts will be translated into proteins. This control affects the length of time it takes for mRNA to be activated and the speed at which cytoplasmic enzymes destroy mRNA.
posttranslational	Before many proteins become functional, they must pass through the cell membrane. A number of control mechanisms affect the rate at which a protein becomes active and the time that it remains functional, including the addition of various chemical groups.

Control Mechanisms in Prokaryotes

- **The *Lac* Operon**
- **The *trp* Operon**

Control Mechanisms in Prokaryotes

- **Operon**: a cluster of genes under the control of one promoter and one operator

- **Operator**: regulatory sequence of DNA to which a repressor protein binds

The *lac* Operon

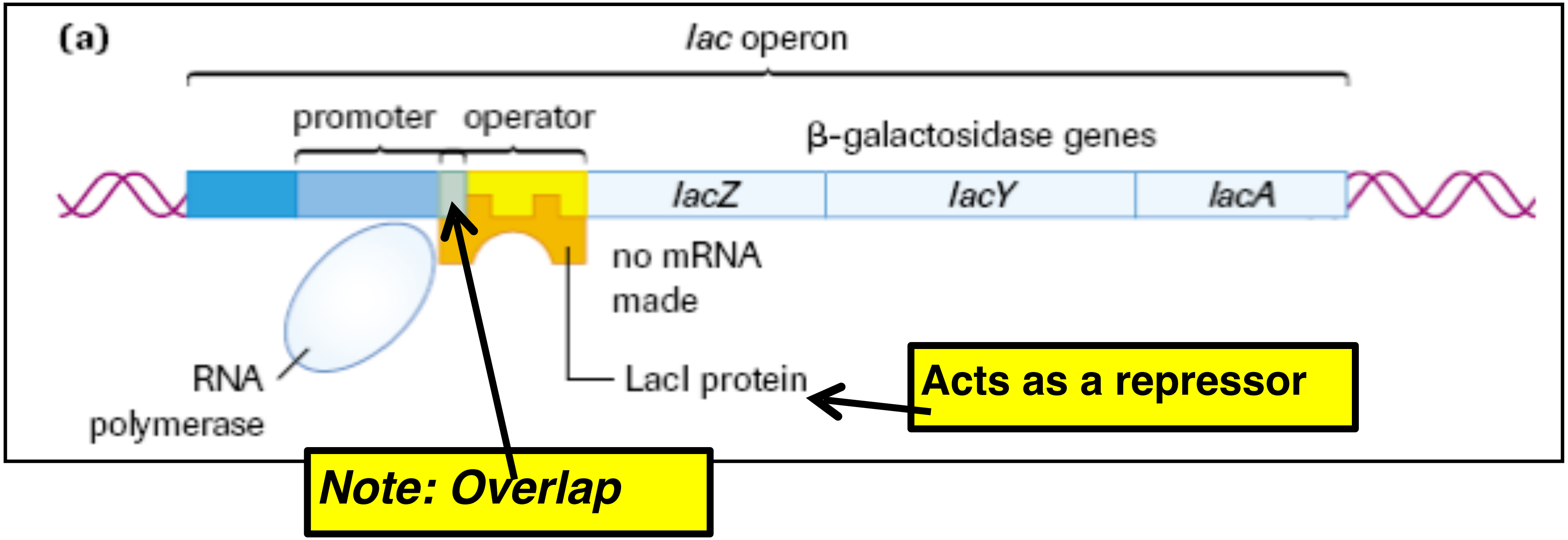
- *E. coli* uses lactose from our digestive tract to grow by using the enzyme **β-galactosidase** to split lactose to glucose and galactose
- When there is no lactose available to break down, E.coli stops the production of **β-galactosidase**
- *E. coli* uses a negative regulation system to control transcription of **β-galactosidase**.
- The gene for **β-galactosidase** is located on an **operon.**

- An **operon** is a grouping of nucleotide sequences of DNA including an operator, a common promoter, and one or more structural genes, which is controlled as a unit to produce messenger RNA (mRNA), by the process of transcription of an RNA polymerase.

- ***Operator:*** Regulatory sequences of DNA to which a repressor protein binds

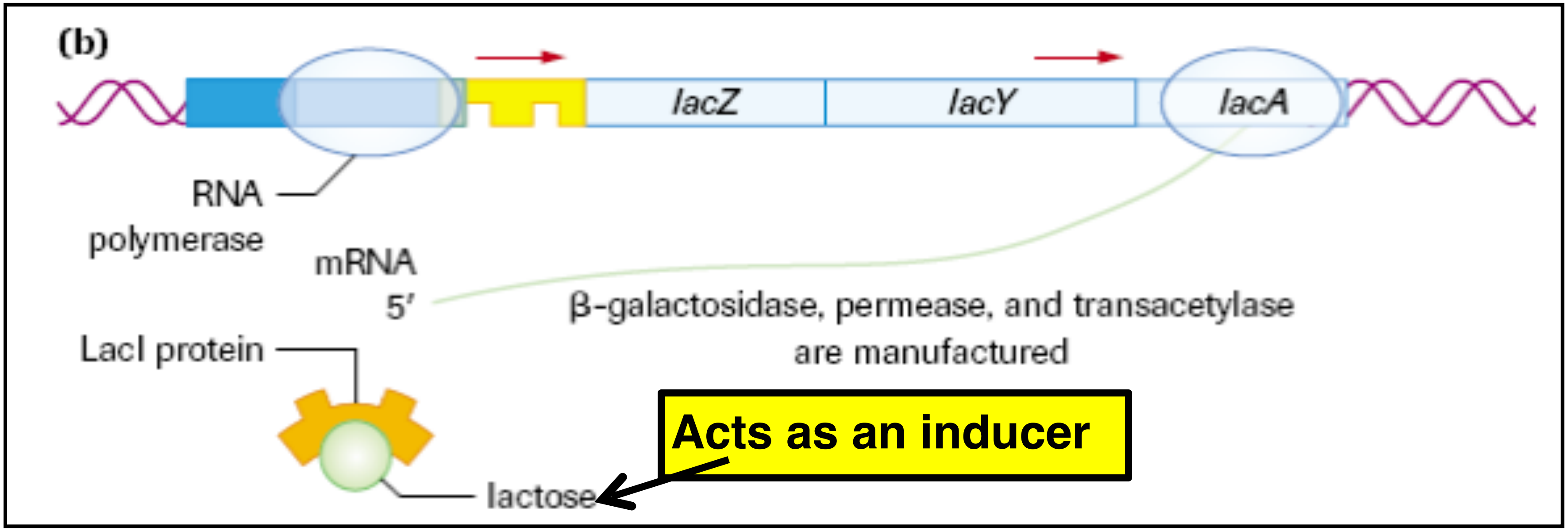
The *lac* Operon

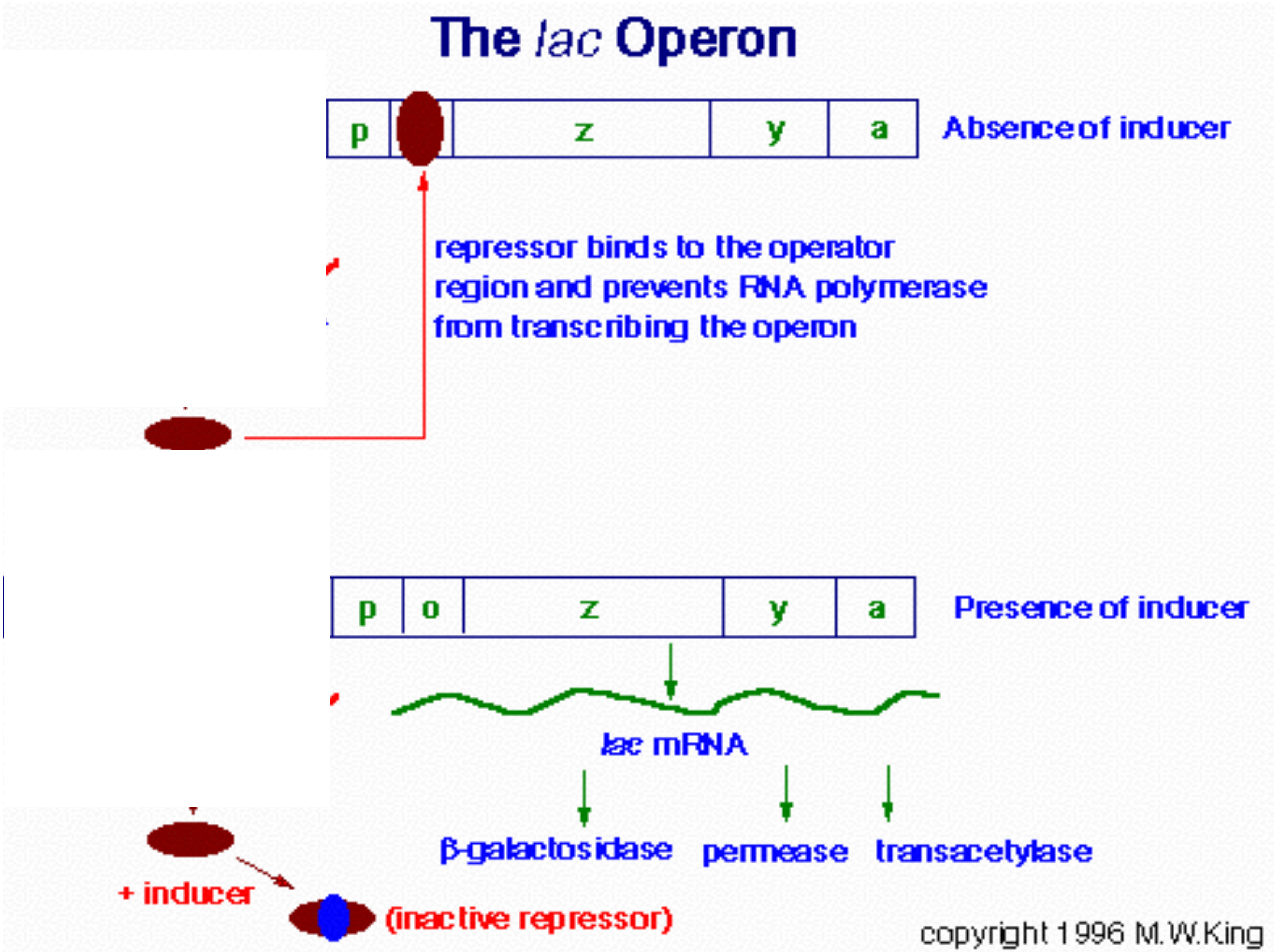
- When lactose is absent, **LacI repressor protein** blocks transcription of *lac* operon genes by binding to the lac operator and partially blocking RNA polymerase.



The *lac* Operon

- Lactose acts as an **inducer** (a chemical that binds to the repressor molecule causing a structural change. Once this structural change takes place in the repressor, it can bind to the operator) by binding to LacI.
- LacI changes its shape and can no longer bind to operator
- this allows transcription of the *lac* operon genes.




The lac Operon
p
z
y
a
Absence of inducer
repressor binds to the operator region and prevents RNA polymerase from transcribing the operon
p
o
z
y
a
Presence of inducer
lac mRNA
β-galactosidase
permease
transacetylase
+ inducer
(inactive repressor)
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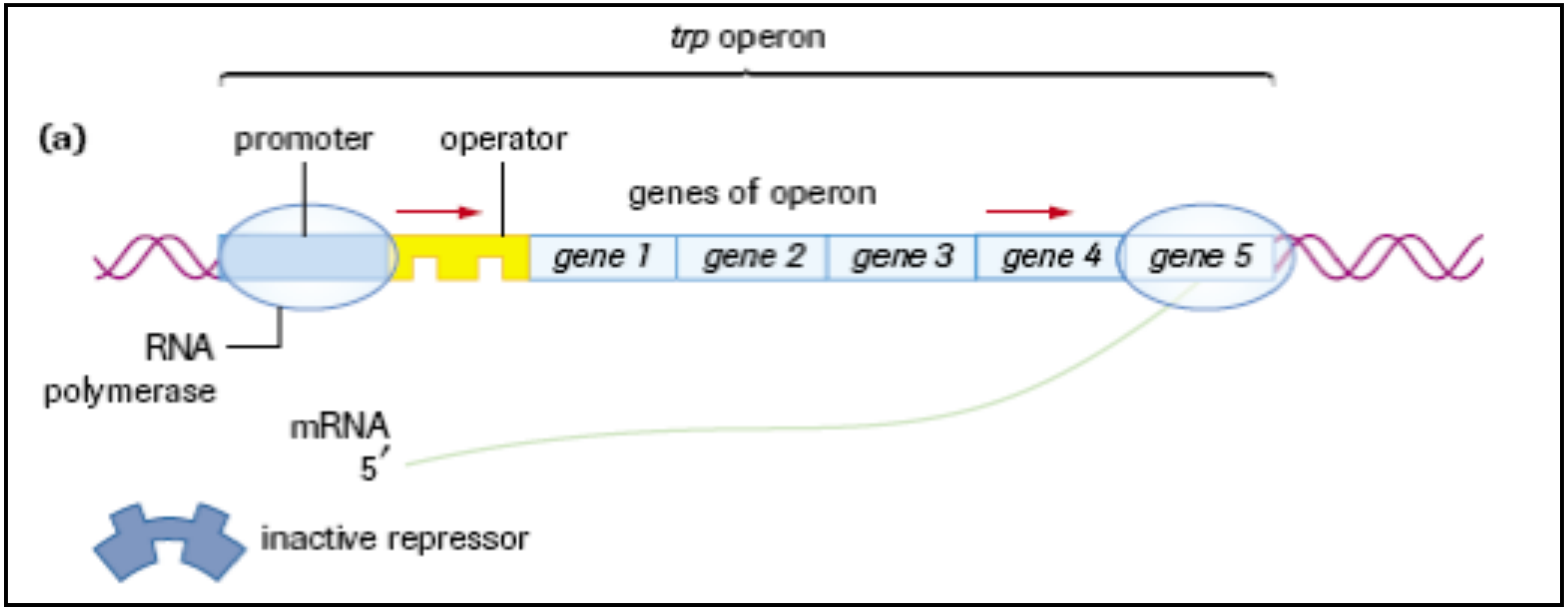
The *trp* Operon

- *E. coli* uses the amino acid tryptophan for the production of protein.
- If *E. coli* can obtain tryptophan from the environment it does not need to make it, so in the presence of tryptophan, the Trp operon is turned 'off'.
- The Trp operon consists of 5 genes that code for 3 enzymes needed to synthesize tryptophan.

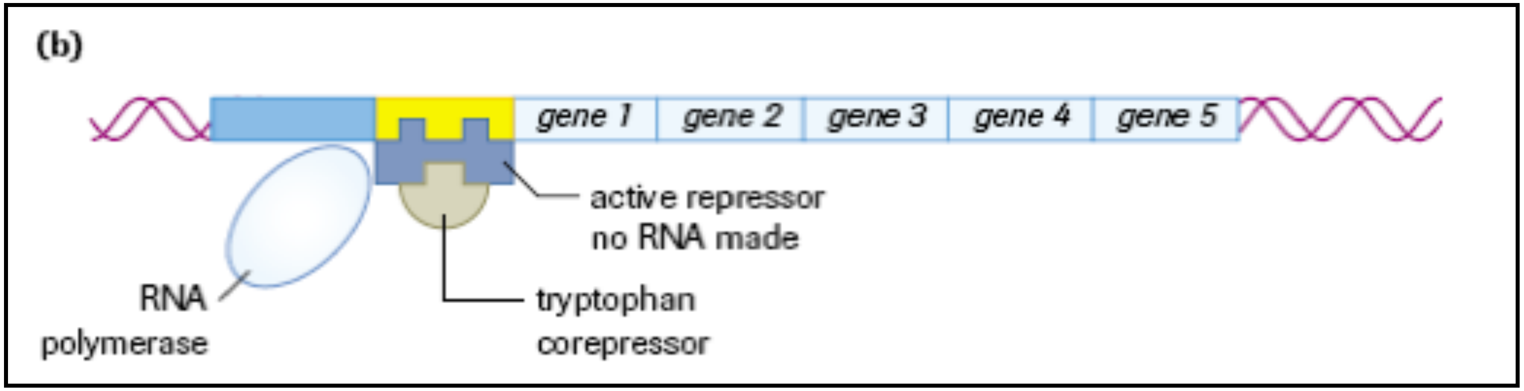
The *trp* Operon

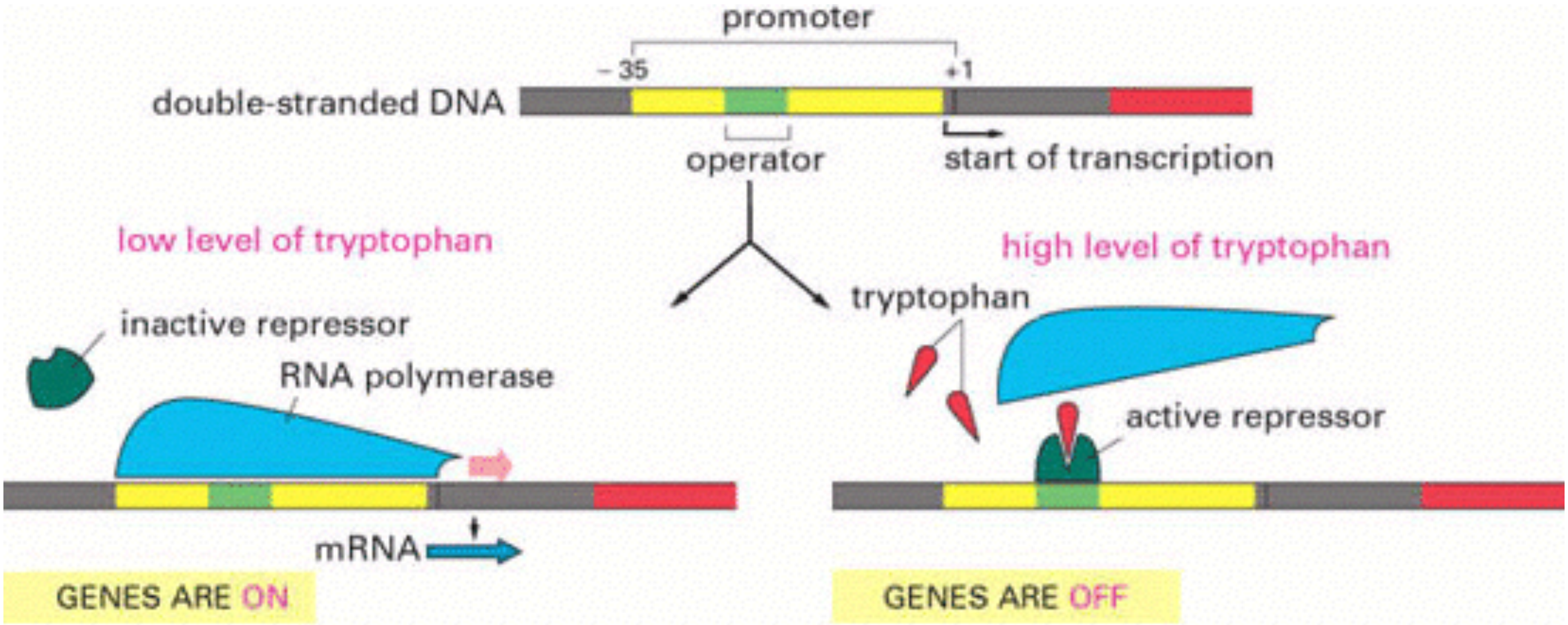
- With no tryptophan around the shape of the ***trp* repressor protein** is such that it cannot bind to the *trp* operator.
- RNA polymerase transcribes *trp* operon genes and tryptophan is produced by *E. coli* .



The *trp* Operon

- Tryptophan binds to the *trp* repressor protein altering its shape.
- The *trp* repressor-tryptophan complex binds to the *trp* operator.
- RNA polymerase is unable to bind to promoter region and the genes are not expressed
- Since tryptophan is needed to inactivate the *trp* operon, it is called a **corepressor**.




promoter
– 35
+1
double-stranded DNA
operator
start of transcription
low level of tryptophan
high level of tryptophan
tryptophan
inactive repressor
RNA polymerase
active repressor
mRNA
GENES ARE ON
GENES ARE OFF

Homework:

- Investigate the Lac Operon in greater detail by exploring the pictures and animation here: "http://vcell.ndsu.edu/animations/lacOperon/index.htm"