Gene Regulation

Everything mostly from Campbell's
Presentation by Laurie Wang, slides by Slidesgo

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Bacterial Regulation

Tryptophan

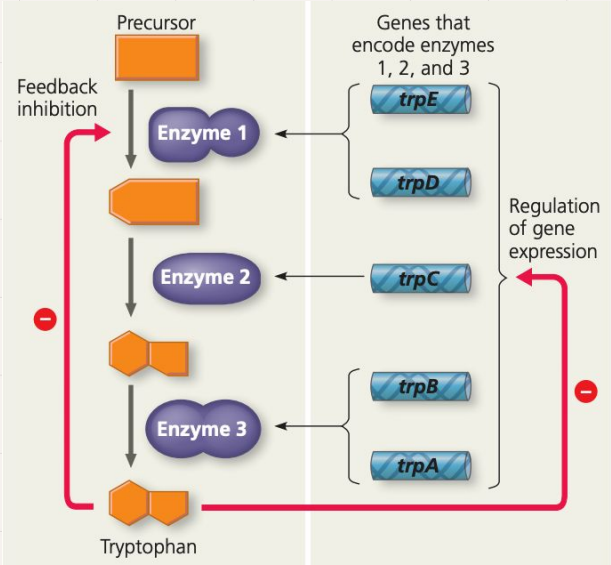
- E. coli in the gut
- Tryptophan in environment = no need to make any
- No tryptophan = needs to make some

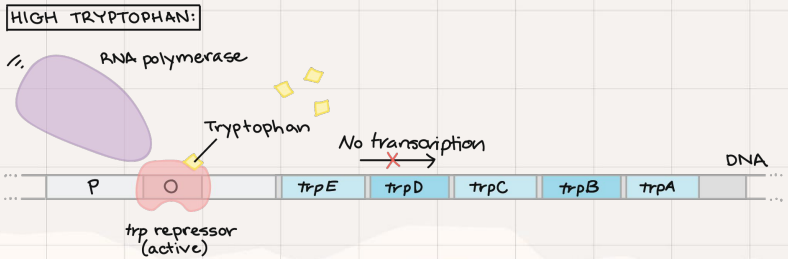
2 Mechanisms:

- **Control activity of existing enzymes**
  - A lot of enzymes can be controlled by chemicals to increase/decrease activity
  - Feedback inhibition – Tryptophan (end product) inhibits the pathway

- **Adjust production level of enzymes**
  - Regulate genes encoding enzymes
  - Cell can stop making tryptophan–making enzymes

Operons





- A bunch of genes with a similar purpose lumped together
- Controlled by the same **operator** (on-off switch) – coordinately controlled
- **Operator control**
  - **Repressor** can switch off
    - Repressor = less expression
    - Encoded by regulatory gene (trpR)
  - **Corepressor** controls repressor
    - Trp helps the repressor bind to the operator

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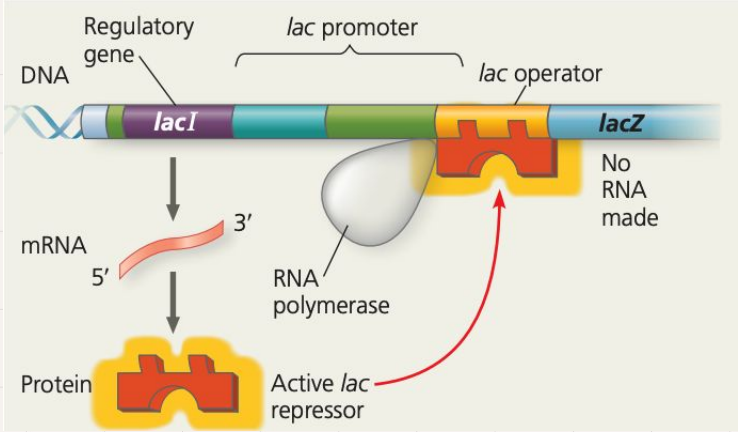
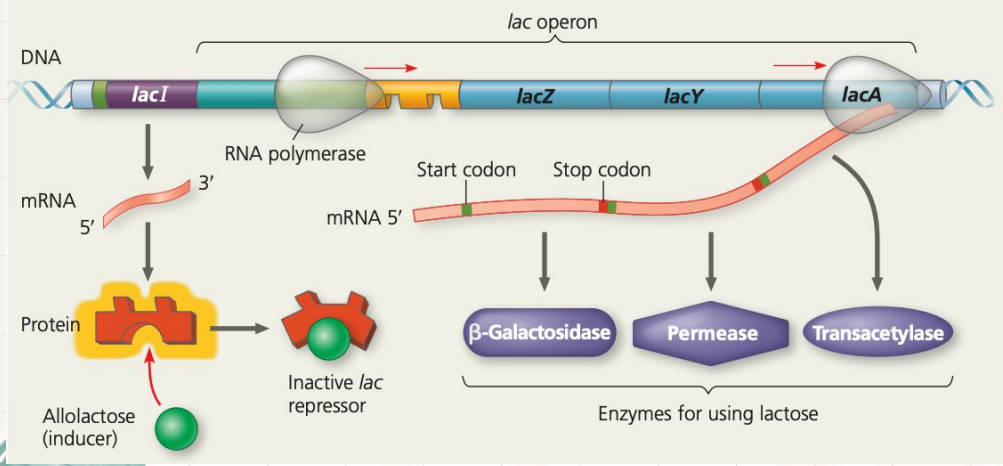
Repressible and Inducible Operons





Repressible – Trp operon - (Repressible enzymes) - Anabolic

- Transcription inhibited when a corepressor (Trp) binds to the regulatory protein

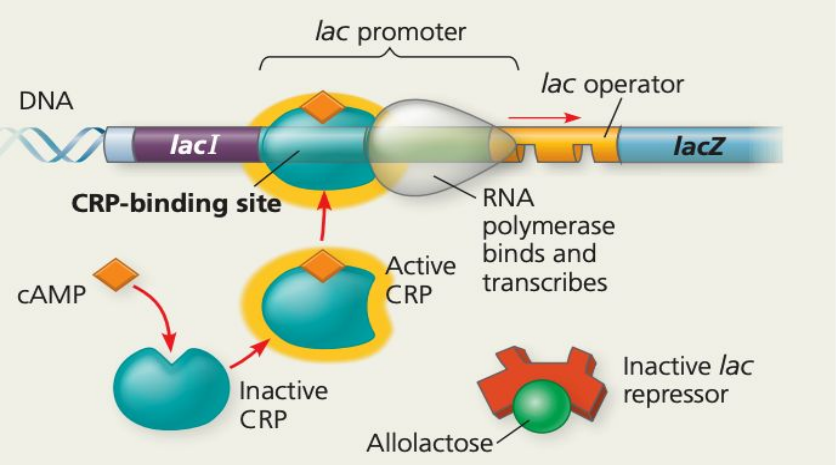
Inducible (Inducible enzymes) - Catabolic

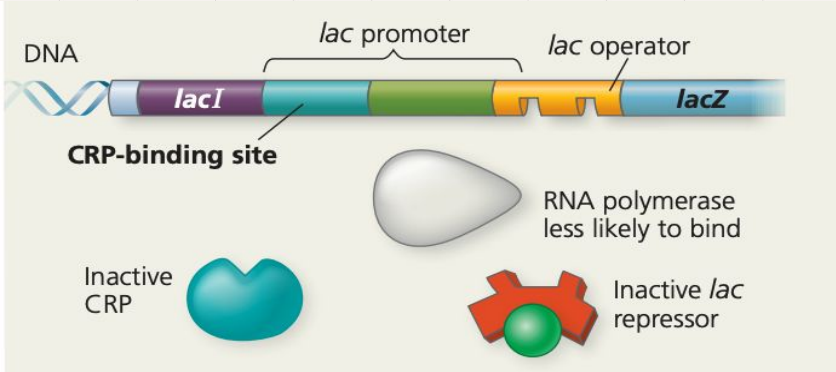
- Transcription stimulated when a molecule interacts with the regulatory protein

Lac operon

- Controls lactose metabolism
  - Beta-galactosidase
- Not necessary when there's no lactose
- The regulatory molecule is an **inducer** (allolactose)
- The repressor protein is bound when there is no lactose

Positive Gene Regulation





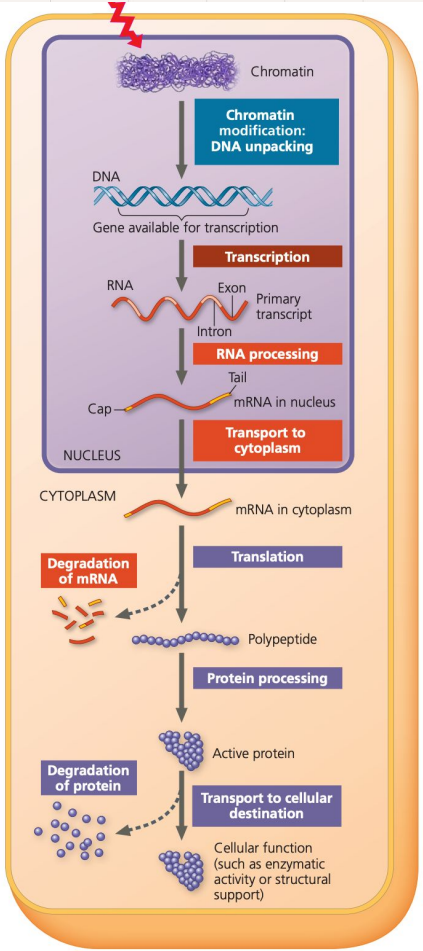
E. coli prefers glucose.

- **Cyclic AMP** (cAMP) signals that there is low glucose
- cAMP binds to **CRP** (CAP), an a**ctivator protein**, which binds to the DNA and helps RNA pol bind
- If high glucose → cAMP concentration falls, CRP detaches, RNA pol binds less efficiently, less transcription
- This controls the rate

02

Eukaryotic Gene Regulation

Regulation Stages



Eukaryotic gene expression is regulated at many stages

- Chromatin
- Transcription
- RNA processing
- Translation vs. Degradation
- Protein processing
- Degradation

Differential gene Expression

- Expression of different genes by cells with the same genome
- Function depends on expressing the right sets of genes

Chromatin

Histone acetylation

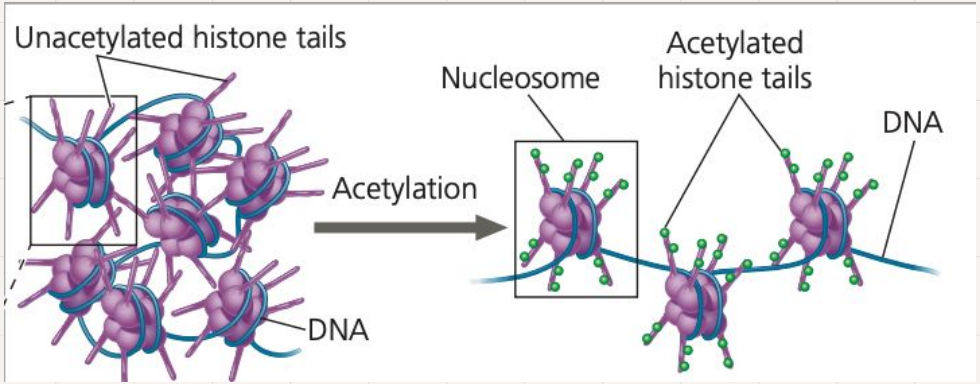
- Increases expression because DNA becomes looser

DNA methylation

- Cytosines have methyls added to them, which decreases expression

Epigenetic Inheritance

- Inheritance of traits not through DNA sequence
- Usually reversible, such as in gamete formation or in a different environment



Transcription

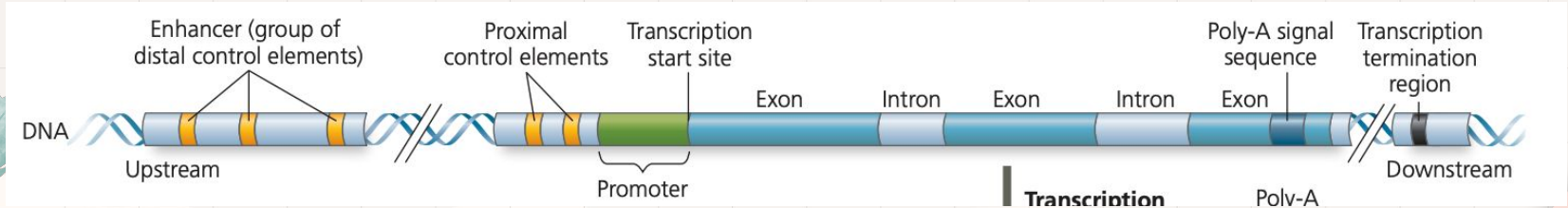
General transcription factors: Necessary for all protein-coding genes
Specific transcription factors: Different for different cell types

Proximal control elements – close to promoter
Distal control elements (groups = **enhancers**) – far from the promoter – DNA loops over

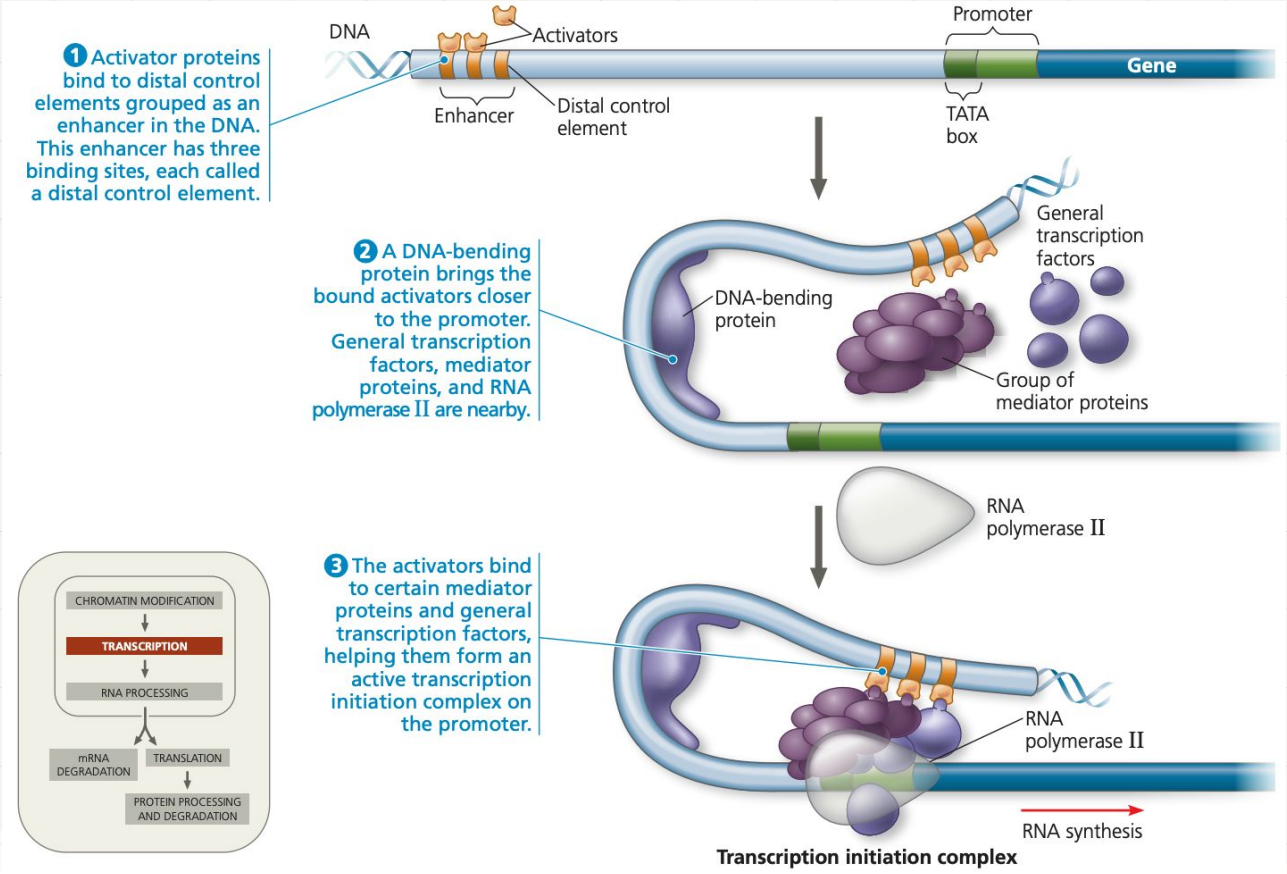
Rate of gene expression influenced by binding of specific transcription factors (activators or repressors) to control elements in enhancers

A combination of certain control elements determine how genes are regulated

Coordinately controlled gene expression – genes have the same combination of control elements

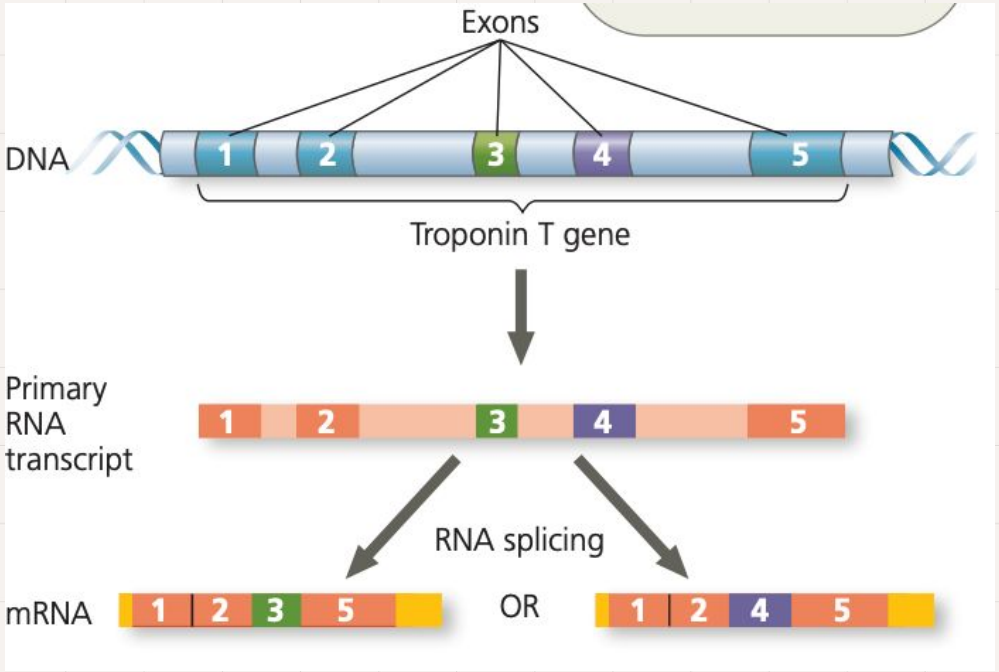


Transcription



RNA Processing

Alternative RNA splicing



Translation + Degradation

- Regulatory proteins can bind to specific sequences in the untranslated region (UTR) to prevent ribosomes from attaching
- **Global mRNA control** – all mRNAs in a cell regulated simultaneously
    - Usually due to activation/inactivation of proteins factors needed for translation

Degradation

- Bacterial mRNA degraded in minutes
    - Allows for quick responses to environmental changes
- Euk mRNA lasts longer
    - Lifespan determined by sequence at 3’ UTR

Protein Processing + Degradation

Processing may be required

- Cleavage of a polypeptide
  - Pro-insulin
- Chemical modifications
  - Phosphate groups to activate/inactivate
  - Glycosylation for membrane proteins
- Transport to destination

Selective degradation determines the protein's lifetime

- Some proteins need to be short-lived
  - Cyclins
- Process
  - Ubiquitin attached to protein
  - Proteasomes recognize the tag and degrade the tagged protein

03 Noncoding RNAs

Short Noncoding RNAs

microRNAs (miRNAs)

- Bind to complementary mRNA
- ~22 nucleotides
- Comes from processing longer RNA
- Forms a complex with proteins and allows the complex to bind to complementary mRNA
- miRNA complex degrades mRNA or blocks translation

Small interfering RNAs (siRNAs)

- Blocking is called RNA interference (RNAi)
- Can induce formation of heterochromatin in yeast

Piwi-interacting RNAs (piRNAs)

- Induces formation of heterochromatin
- Blocks expression of transposons
- Come from single-stranded precursor
- Re-establish appropriate methylation patterns during gamete formation

Long Noncoding RNA

lncRNAs

- <200 nucleotides long
- One is responsible for X chromosome inactivation
- May act as a scaffold to bring DNA, proteins, and RNA together

04

Differential Gene Expression

Basics

- **Division** – mitosis
- **Differentiation** – how cells become specialized
- **Morphogenesis** – how organisms get a shape

- Depend on varying shape, motility, etc. of cells
- Is caused by different gene regulation in different cell types

Cytoplasmic Determinants and Inductive Signals

- mRNAs, proteins, organelles, etc. are not distributed evenly in an egg

Cytoplasmic determinants – maternal substances in egg that influence the course of early development

- Division of the zygote results in daughter cells being exposed to different cytoplasmic determinants

Induction – Signaling between embryonic cells that are close together, causing changes

- Usually sends cell down specific developmental path
- Important in specialized cell types

More

Differentiation – tissue-specific proteins enable differentiated cells to carry out specialized roles

Pattern formation (spatial organization of tissues and organs) – begins in early embryo

Positional information – helps cells locate themselves relative to other cells and the body's axes

- **Morphogen** (from maternal effect genes) gradients determine body axes in Drosophila
    - **Bicoid** protein determines anterior-posterior axis

05

Cancer and Gene Regulation

Types of Genes Associated with Cancer

Oncogenes

- Come from proto-oncogenes, which usually stimulate normal cell growth and division
- Becomes an oncogene usually from an increase in the proto-oncogene's protein product or the activity of the protein
- Genetic changes that convert proto-oncogenes to oncogenes
  - Epigenetic changes
    - Abnormal chromatin condensation
    - Looser chromatin in a region that usually has lower expression may lead to high levels of expression for a proto-oncogene in that region
  - Translocations
    - Pieces of chromosomes broke off and rejoined incorrectly
    - A proto-oncogene may have ended up near an especially active promoter or control element
  - Amplification
    - Gene duplication increases the number of copies of the proto-oncogene
  - Point mutation
    - Gene product could become more active or resistant to degradation

Types of Genes Associated with Cancer

Tumor-suppressor genes

- Normal products inhibit cell division
- Mutations that decrease activity may lead to cancer
- Functions
  - DNA repair
  - Control adhesion of cells to each other/extracellular matrix
  - Part of cell-signaling pathways that inhibit the cell cycle

Interference with Normal Cell-Signaling Pathways

ras Gene

- Codes for the Ras protein
  - G protein that controls a signaling cascade caused by a growth factor
  - Ends in synthesis of a protein that stimulates cell cycle
  - Mutations may lead to hyperactivity → kinase cascade triggered even in absence of growth factor

p53 Gene

- Tumor suppressor gene
- Encodes transcription factor that promotes synthesis of cell cycle-inhibiting proteins
- “The guardian angel of the genome”
- Activates several other genes once activated, giving time to repair DNA
- Helps activate DNA repair genes
- Activates apoptosis genes if DNA damage can’t be repaired

Questions

Which of the following best describes the repressor protein in the lac (read as: LACK) operon:
W) uncompetitive inhibitor
X) structural protein
Y) regulatory protein
Z) transcriptional factor

Which of the following is the primary difference in regulation between the lactose and tryptophan operons:
W) tryptophan activates its repressor and lactose leads to an inactive repressor
X) when tryptophan is present, the repressor is inactive and the opposite is true for allolactose in the lac operon
Y) allolactose is considered a co-repressor whereas tryptophan is actually an inducer
Z) when tryptophan is not present, the co-repressor is able to inactivate the promoter directly

Which of the following cellular phenomena uses double-stranded RNA with the same or similar sequence to a gene to target that gene for inhibition of transcription and translation?

W) RNA interference
X) Transposition
Y) RNA editing
Z) Alternative splicing

In the lab, you engineer a gene so that it is specifically expressed in pancreatic cells. Which of the following aspects of the gene did you likely adjust?

W) Intron sequences
X) 5’ [5 prime] UTR sequences
Y) Translational start sequences
Z) Promoter sequences

2018

37. Which of the following is incorrect about operons?

A. Operons can be switched off with a repressor.
B. The lac operon is an inducible operon.
C. In the presence of lactose and glucose, the lac operon will not be repressed.
D. CAP is an activator of transcription when not bound to cAMP.
E. A mutation in the operator of the trp operon can lead to overproduction of tryptophan.

2017

10. The progression of cancer is often driven by genetic and epigenetic alterations. Which of the following is not likely to contribute to tumorigenesis?

A. Loss-of-function mutation in the p53 gene.
B. Upregulation of pro-apoptotic proteins.
C. Duplication of the telomerase gene.
D. Increased secretion of growth factors.
E. Moderately high level of oxidative stress.

2013

3. Which of the following correctly describes how the lifespan of a protein is regulated?

A. The part of the sequence coded for by the UTR tags it for destruction.
B. Giant protein complexes called ubiquitins destroy proteins after they have remained in the cell for a certain time.
C. Proteins are methylated over time; heavily methylated proteins are destroyed by proteasomes.
D. Proteins are tagged with ubiquitins, which are recognized by proteasomes; the proteasomes destroy the proteins.
E. Proteins tagged with methyl groups are destroyed by ubiquitins.

2013

7. Which of the following is a way in which the cell increases gene expression in the nucleus?

A. Acetylation of histone tails
B. DNA methylation
C. Locating a gene within heterochromatin
D. Dephosphorylating DNA
E. Alternative splicing

2013

35. Which of the following is correct?

A. Acetylation of histones facilitates expression of the DNA associated with the acetylated histone.
B. Methylation of DNA facilitates expression.
C. G proteins attaching to histones facilitate expression of DNA.
D. Deacetylation of histones facilitates expression of DNA wrapped around the acetylated histone.
E. Methylation of histones facilitates expression of DNA wrapped around the acetylated histone.