

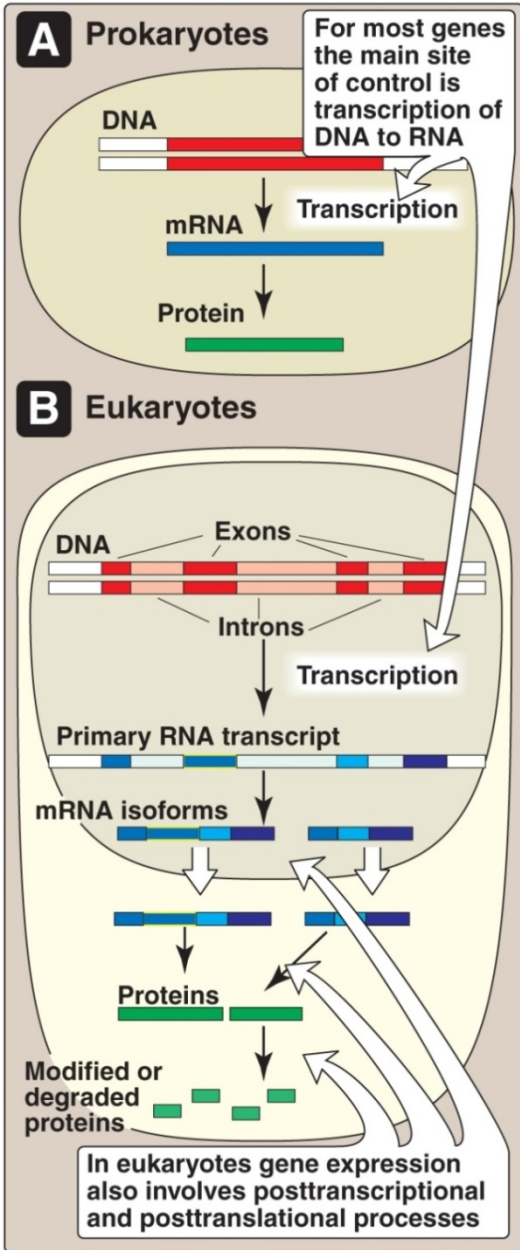
TOPIC 35:

REGULATION OF GENE EXPRESSION

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Sep/2012

Control of gene expression



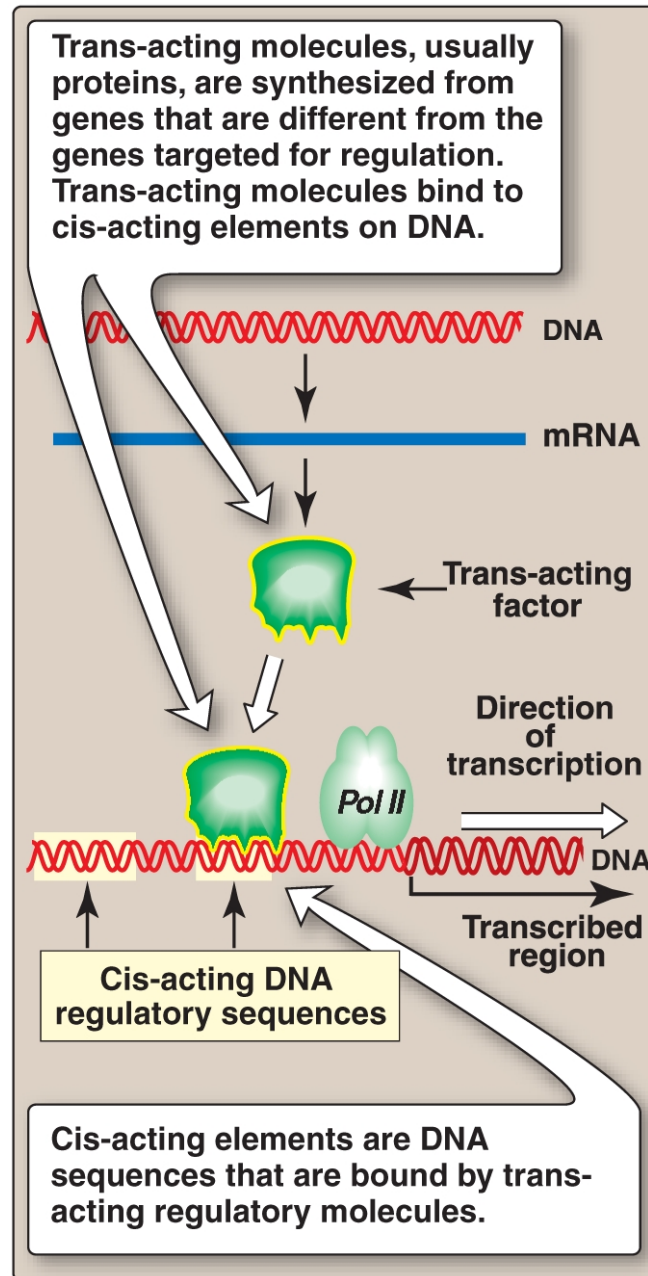
Constitutive genes: housekeeping

Regulated genes: under some conditions

Operon: DNA + proteins

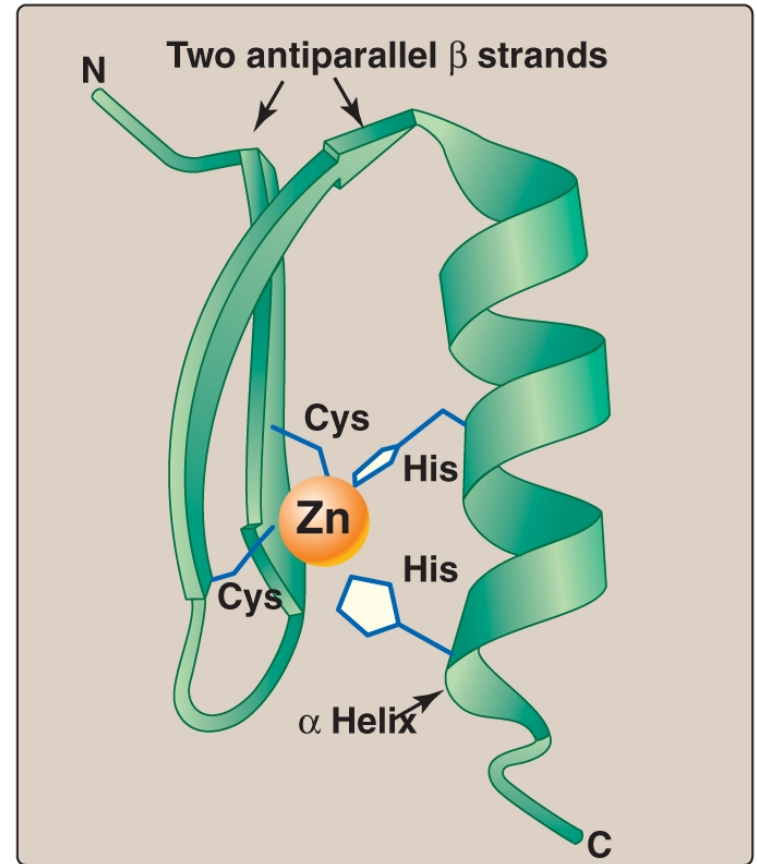
Polycistronic: genes involved in a particular process

Cis-acting elements and trans-acting molecules

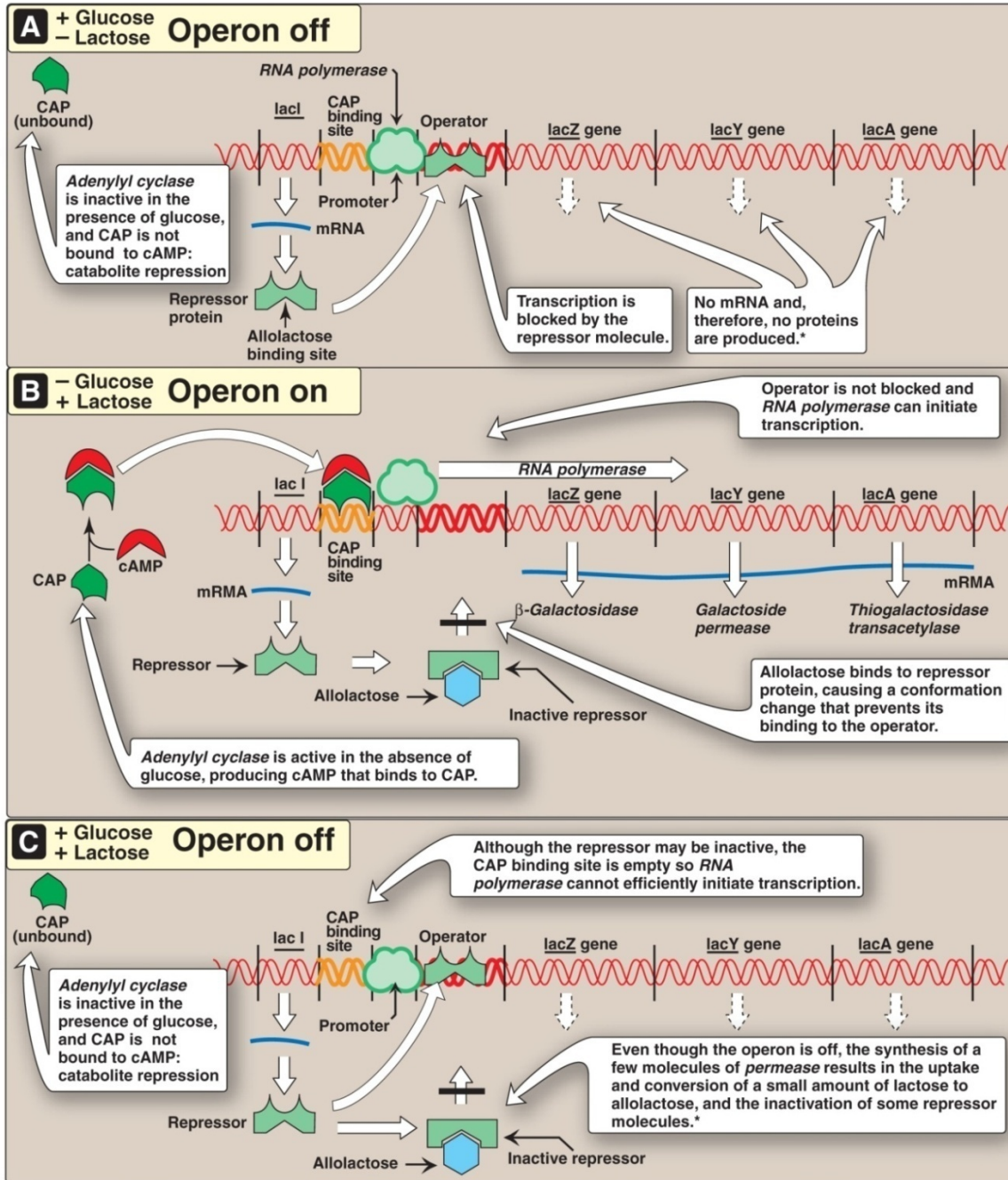
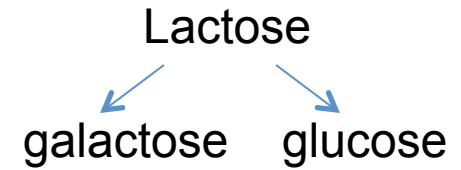


Common motifs in proteins that binds to DNA:

1. Zinc finger domains
2. Leucine zipper
3. Helix-turn-helix



The lactose operon of *E. Coli*

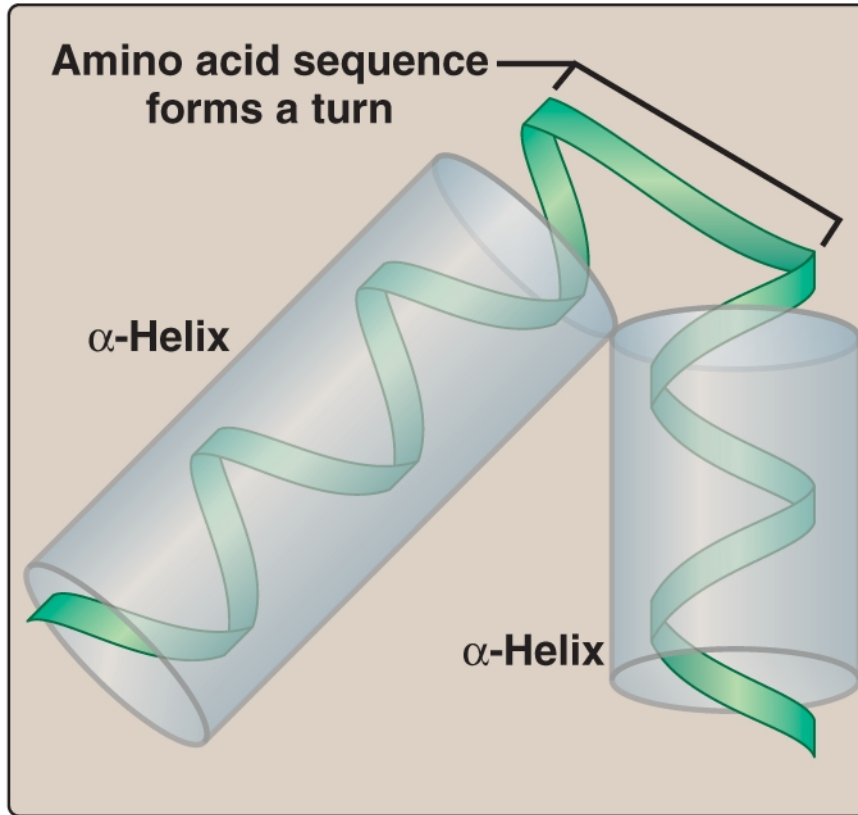


LacZ: β -galactosidase
lacY: permease
lacA: thiogalactoside transacetylase

lacI: Repressor
cAMP: Cyclic AMP
CAP: Catabolite gene activator protein
Allolactose: Inducer

A: negative regulation
 B: positive regulation
 C: catabolite repression

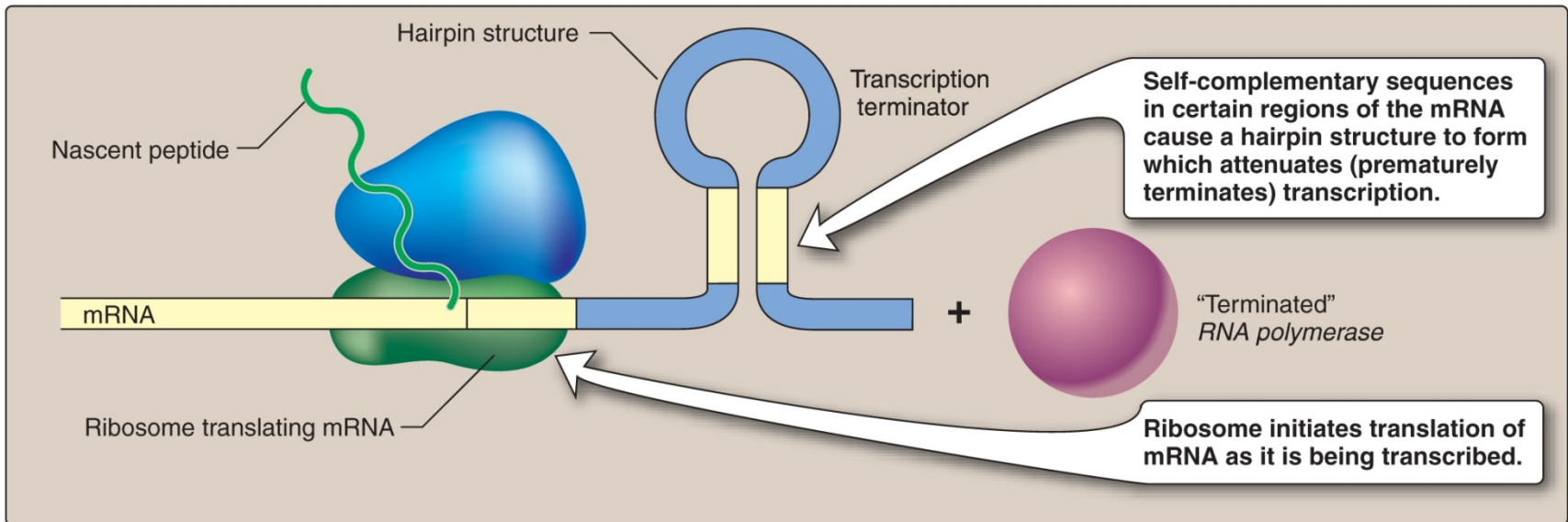
The LacI repressor protein contains a helix-turn-helix motif



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LacI expression is constitutive

Attenuation of transcription of the Trp operon when tryptophan is plentiful



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Negative regulation: Trp binds to repressor and then their binds to operator: no proteins synthesis

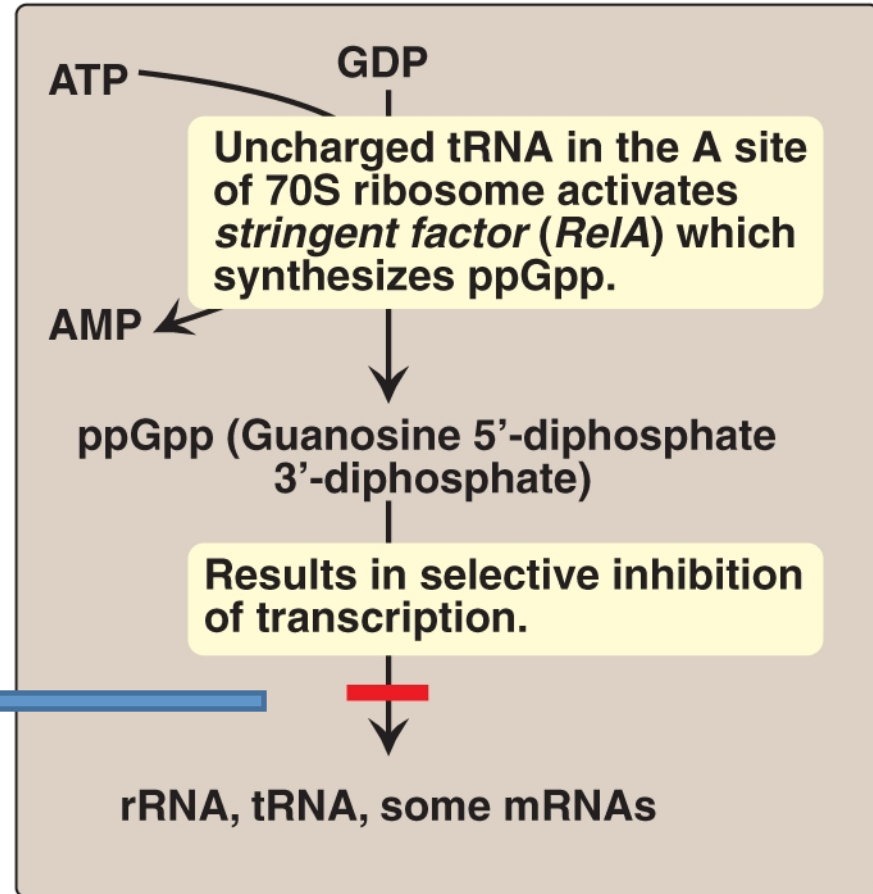
Positive regulation: The repressor can not binds to the operator: protein synthesis

Attenuation: Negative regulation. At the RNA level. Rho-independent termination.

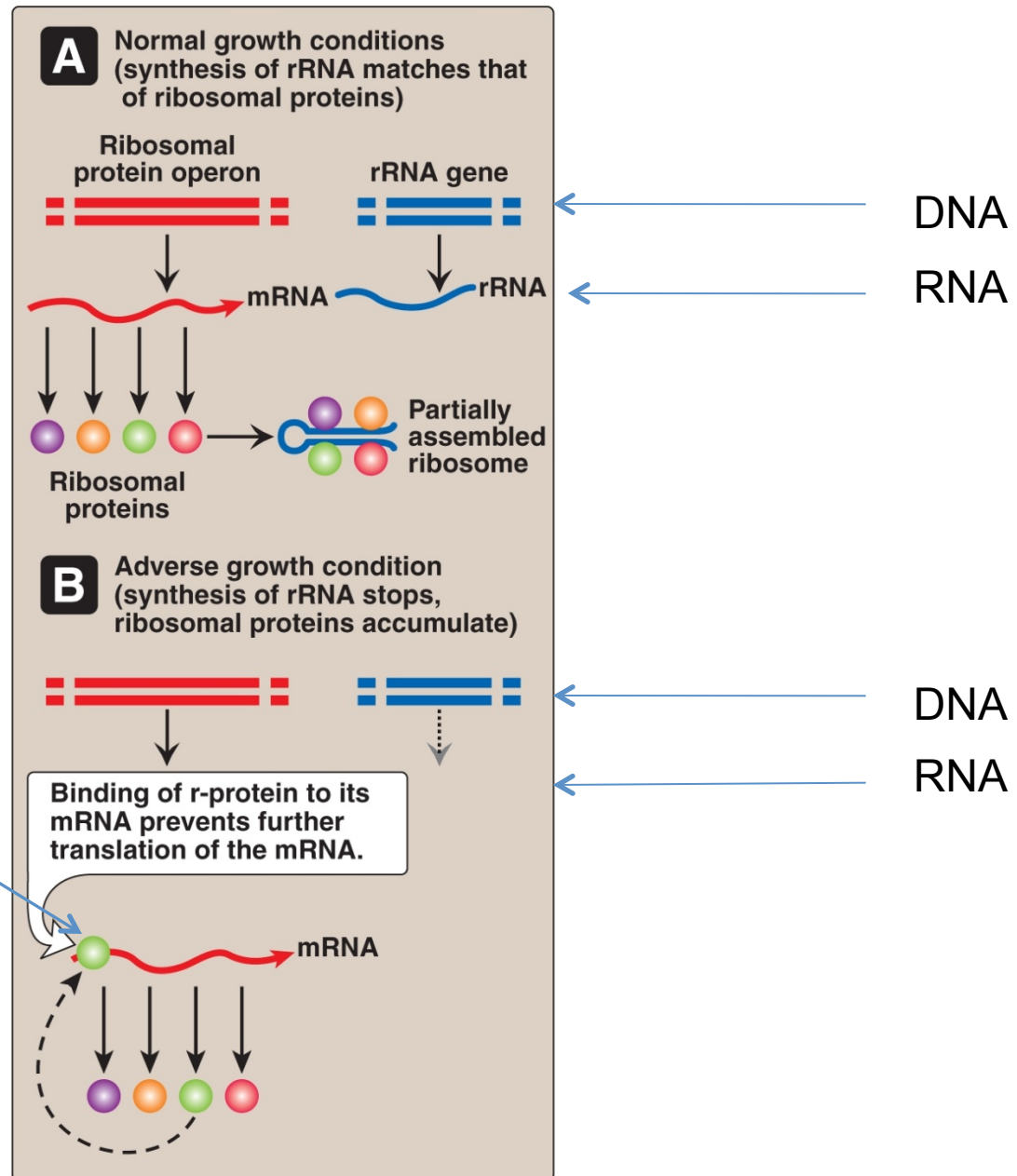
Regulation of transcription by the stringent response to amino acid starvation

No amino acids
↓
No protein synthesis

mRNA for amino acid biosynthesis is not inhibited



Regulation of translation by an excess of ribosomal proteins

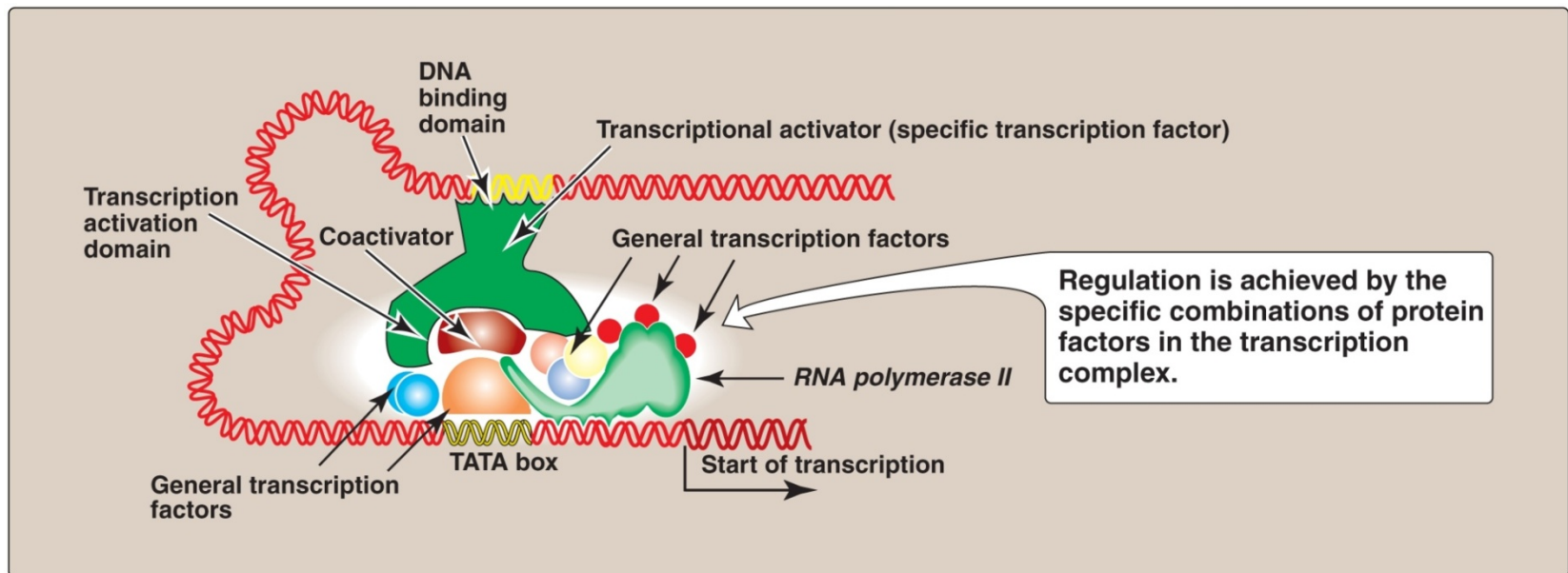


This protein binds to the Shine-Delgarno sequence located upstream of the initiating AUG codon.

Regulation of gene expression in Eukaryotes

- Transcriptional
- Post-transcriptional
 - Alternative splicing
 - RNA stability
 - Translational efficiency

Combinatorial control of transcription in eukaryotes



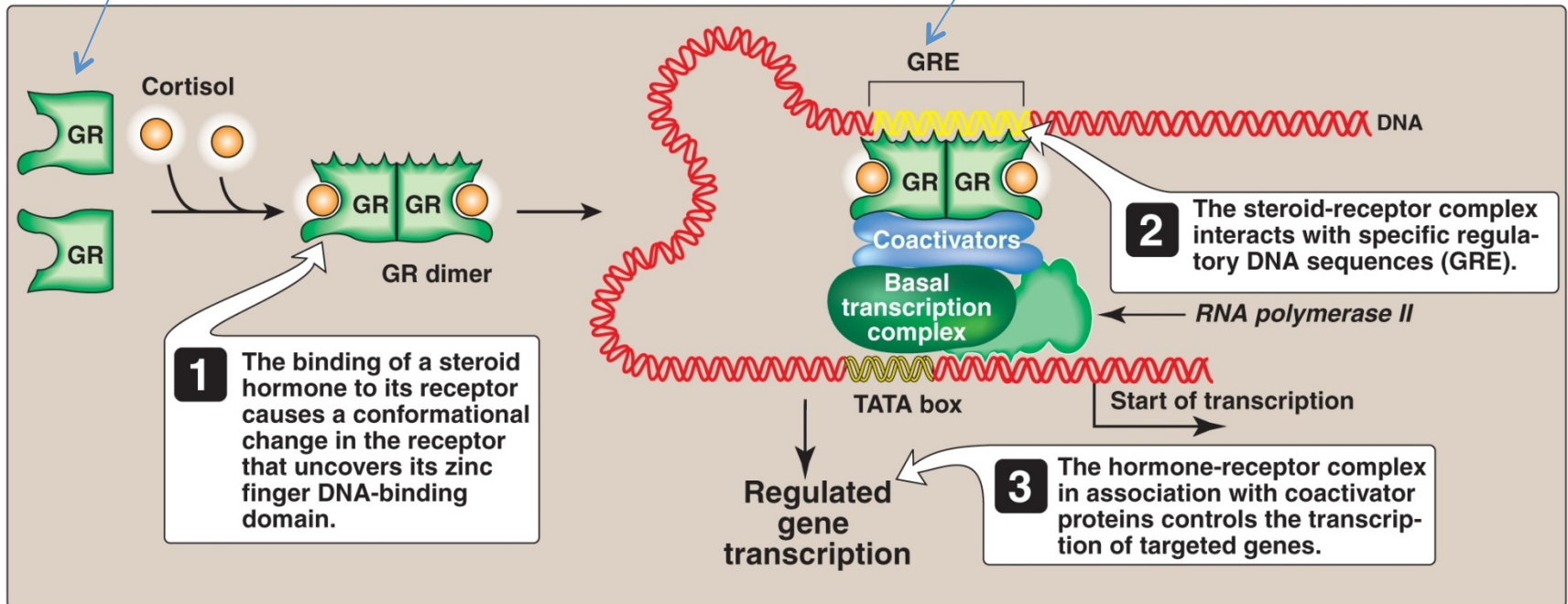
The signal to activate transcription can be initiated by intracellular or cell surface receptors

1. Transcriptional regulation by intracellular steroid hormone receptors

Nuclear receptor

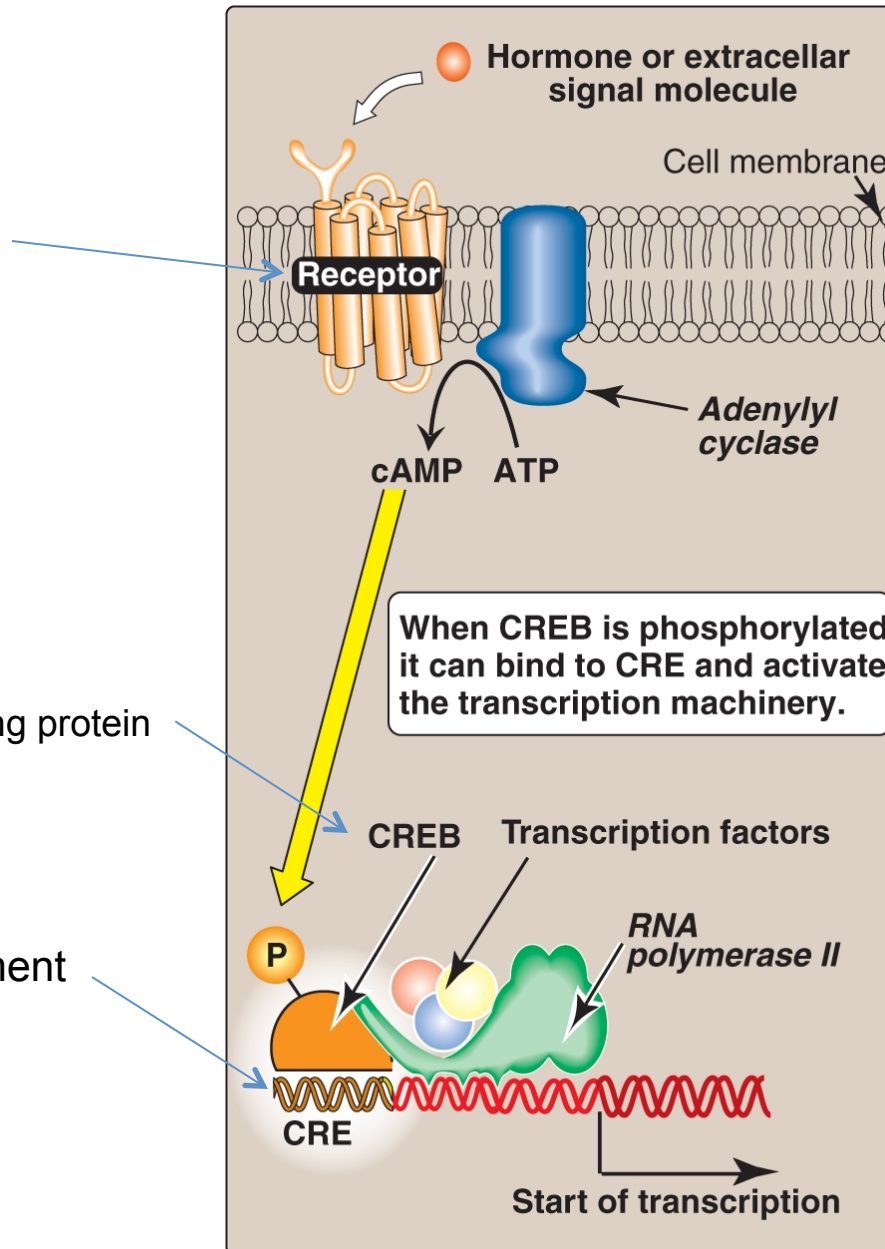
- Glucocorticoids
- Sex hormones
- Mineralocorticoid
- Vitamin D
- Retinoic Acid

Glucocorticoid-response elements (an enhancer)



2. Transcriptional regulation by receptors located in the cell membrane

Receptors for:
Insulin
Epinephrine
Glucagon



cAMP-response element binding protein

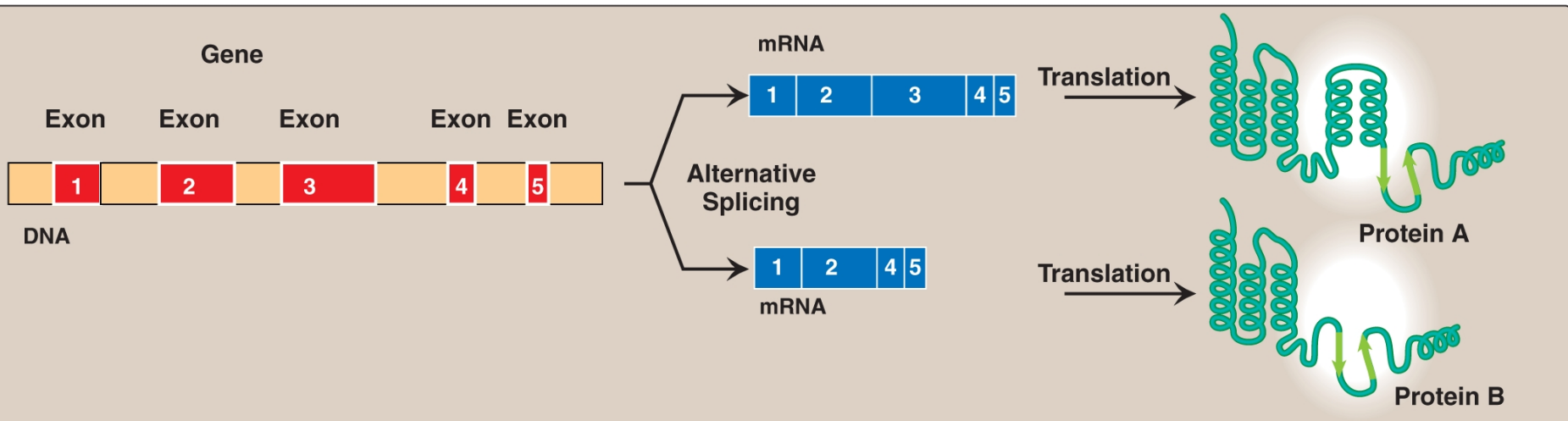
cAMP-response element

Co-transcriptional Regulation

- Capping at the 5' -end
- Poly-A at the 3'
- Splicing

Alternative splicing

30,000 genes
↓
100,000 proteins



Post-transcriptional regulation

- RNA editing
- RNA stability
- Micro-RNA

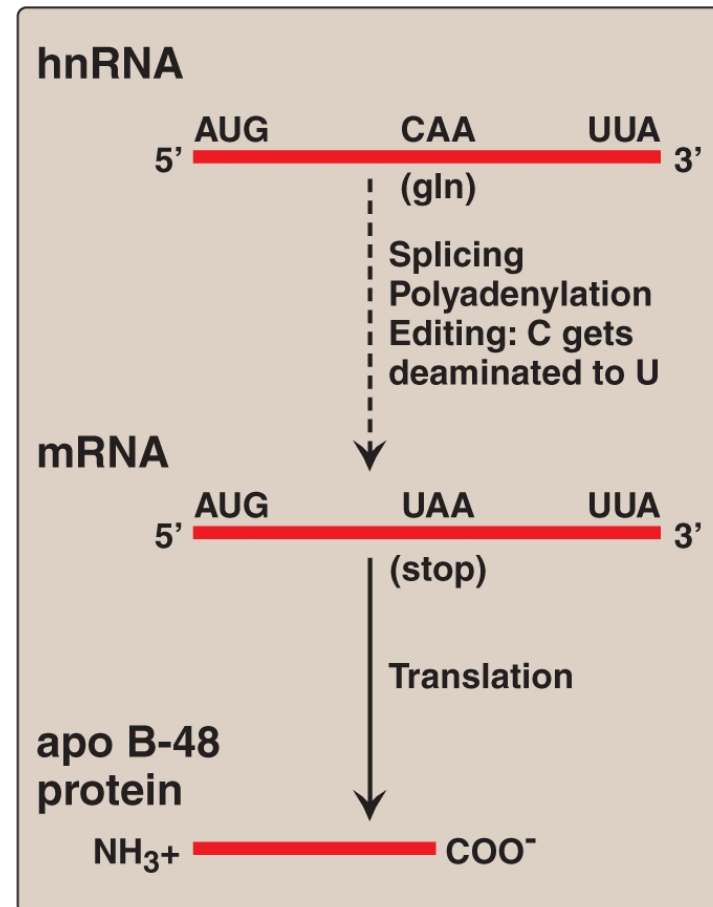
RNA editing: one base in the mRNA is altered

Apoprotein B: chylomicrons and VLDP

Apo B-48
Apo B-100

Liver: only B-100
Intestine: B-100 and B-48

- In some RNAs more than 50% of adenosine residues are modified.
- A to I modifications are more frequent.
- Modifications are performed by ADARs (adenosine deaminase that act on RNA).



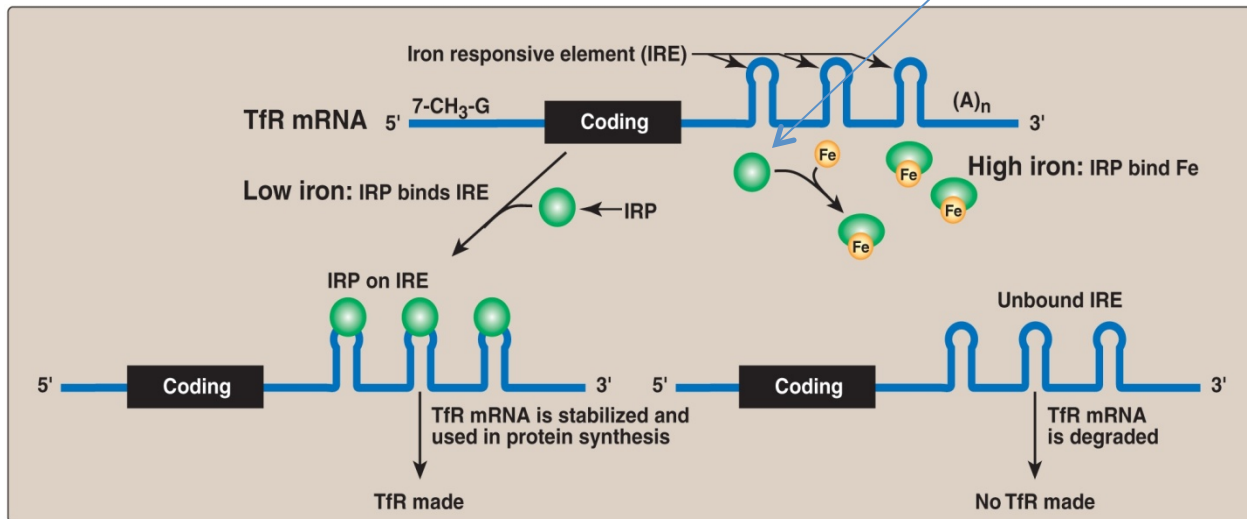
RNA stability: How long time the mRNA remains in the cytosol

Iron metabolism

Transferrin (plasma protein: iron transporter)

↓
Transferrin receptors (TfRs)
(cell membrane)

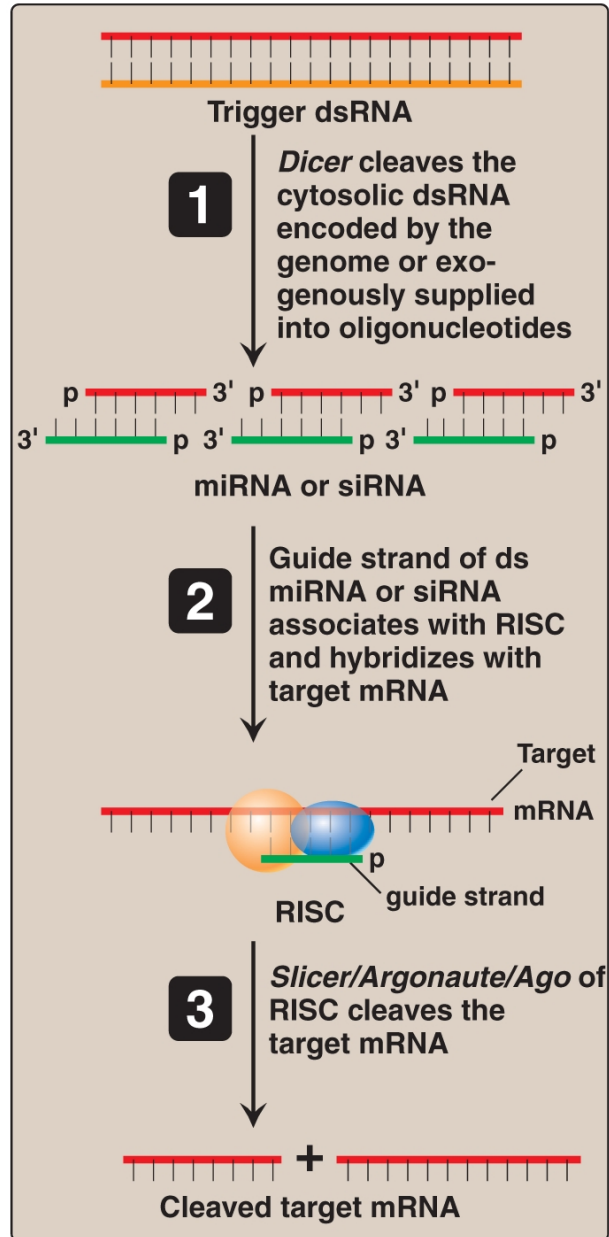
Trans-acting iron regulating proteins
(IRP)



Low iron: IRP binds IRE:
TfR mRNA is stabilized.

High iron: IRP binds to Fe:
TfR mRNA is degraded.

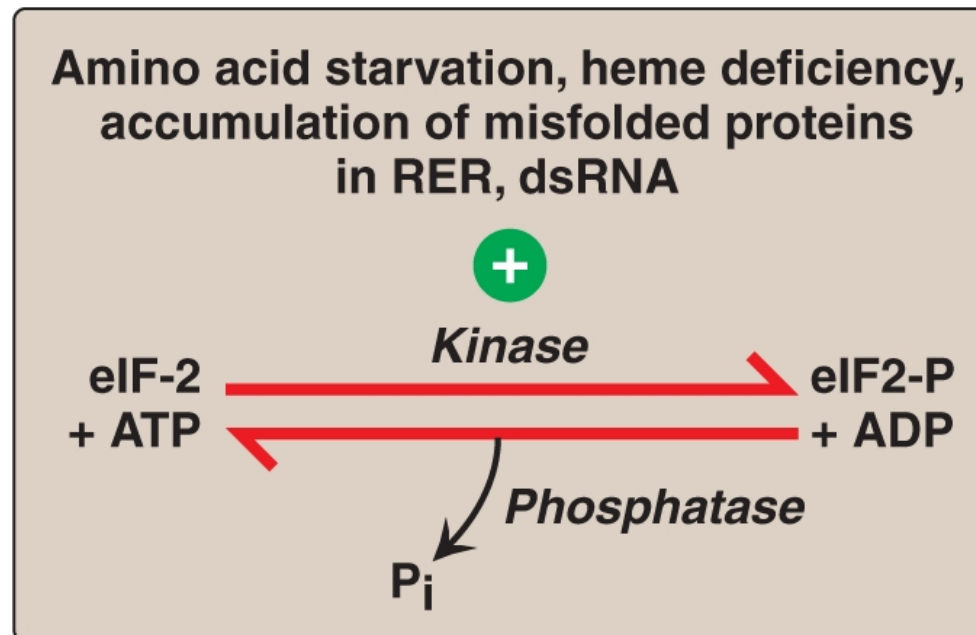
RNA interference: degrade or inhibit mRNA: no protein is produced



RNA translation: protein synthesis

eIF-2: eukaryotic translation initiator factor

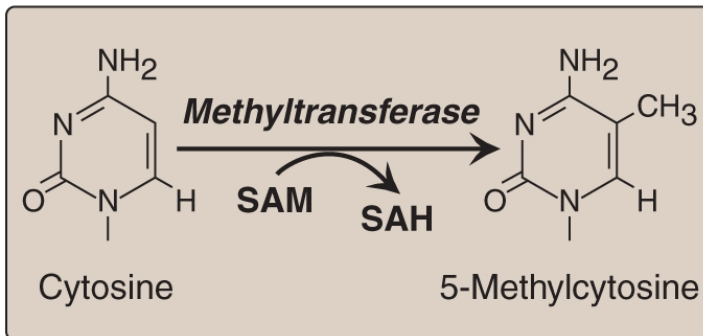
When eIF-2 is phosphorylated inhibits the initiation step of translation



Regulations by modifications to DNA

1. Access to DNA
2. Amount of DNA
3. Arrangement of DNA
4. Mobile DNA elements

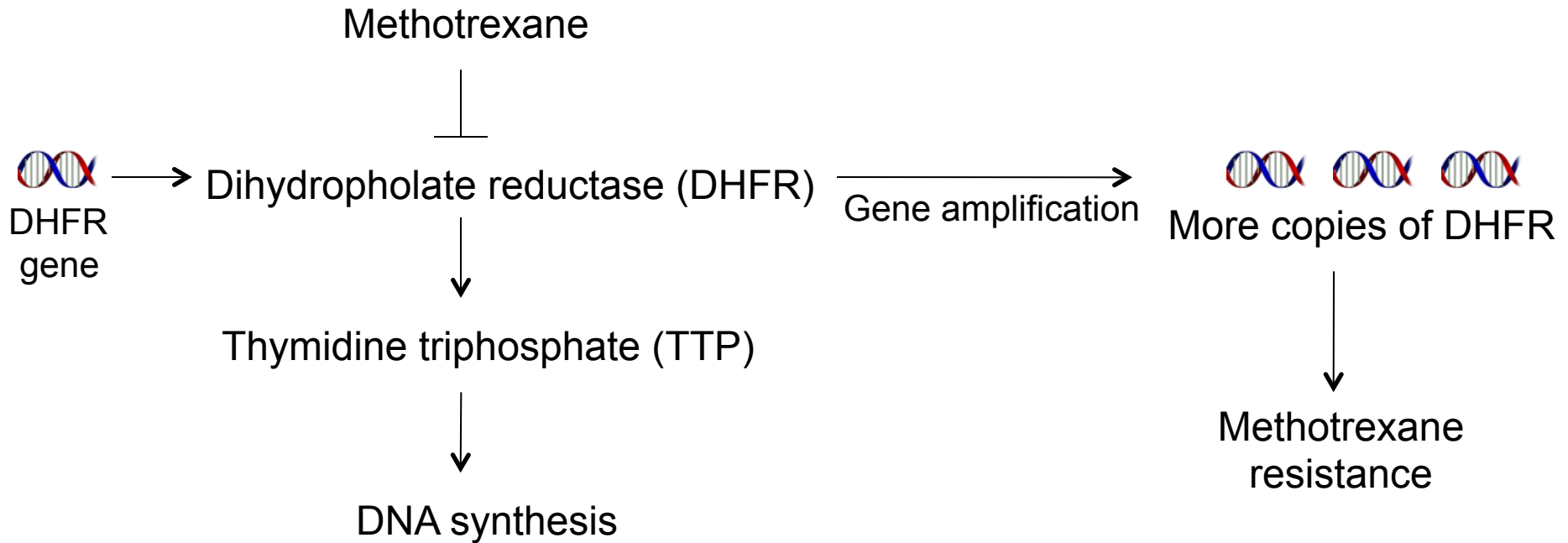
1. Access to DNA: chromatin decondensed (euchromatin) vs. condensed (heterochromatin).



The methylation of cytosine in eukaryotic DNA: DNA hypermethylation (CpG island: silencing gene expression).

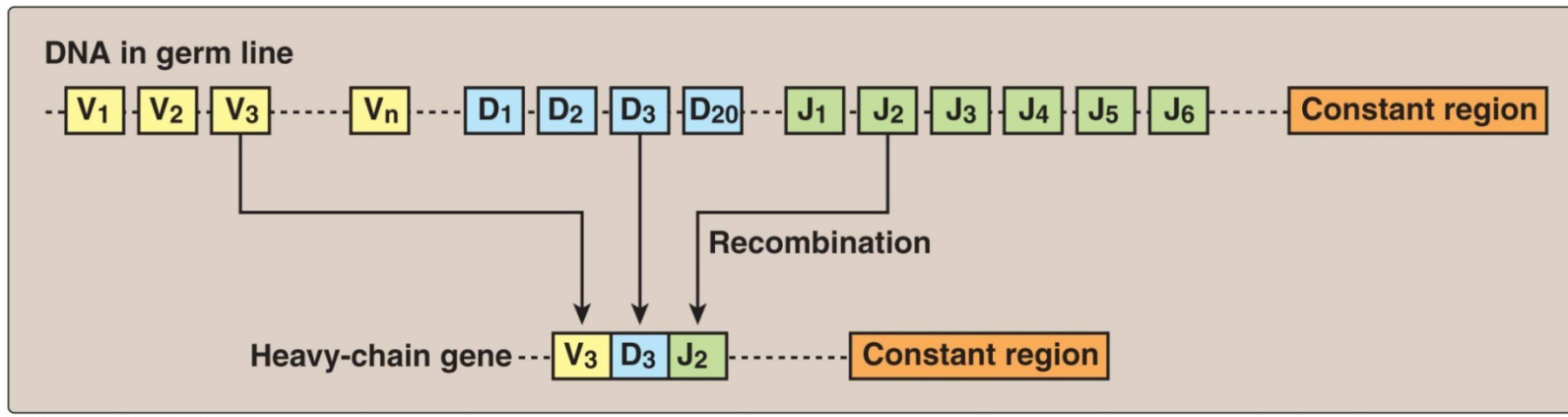
2. Amount of DNA

Gene amplification



3. Arrangement of DNA

DNA rearrangements in the generation of immunoglobulins



Immunoglobulins: two light and two heavy chains

Each chain have variable and constant amino acids sequence

Variable: combination of variable (V), diversity (D) and joining (J)

4. Mobil DNA elements

Transposons: DNA sequences that move randomly in the same or to a different chromosome.

Retrotransposons: involve a DNA intermediate

