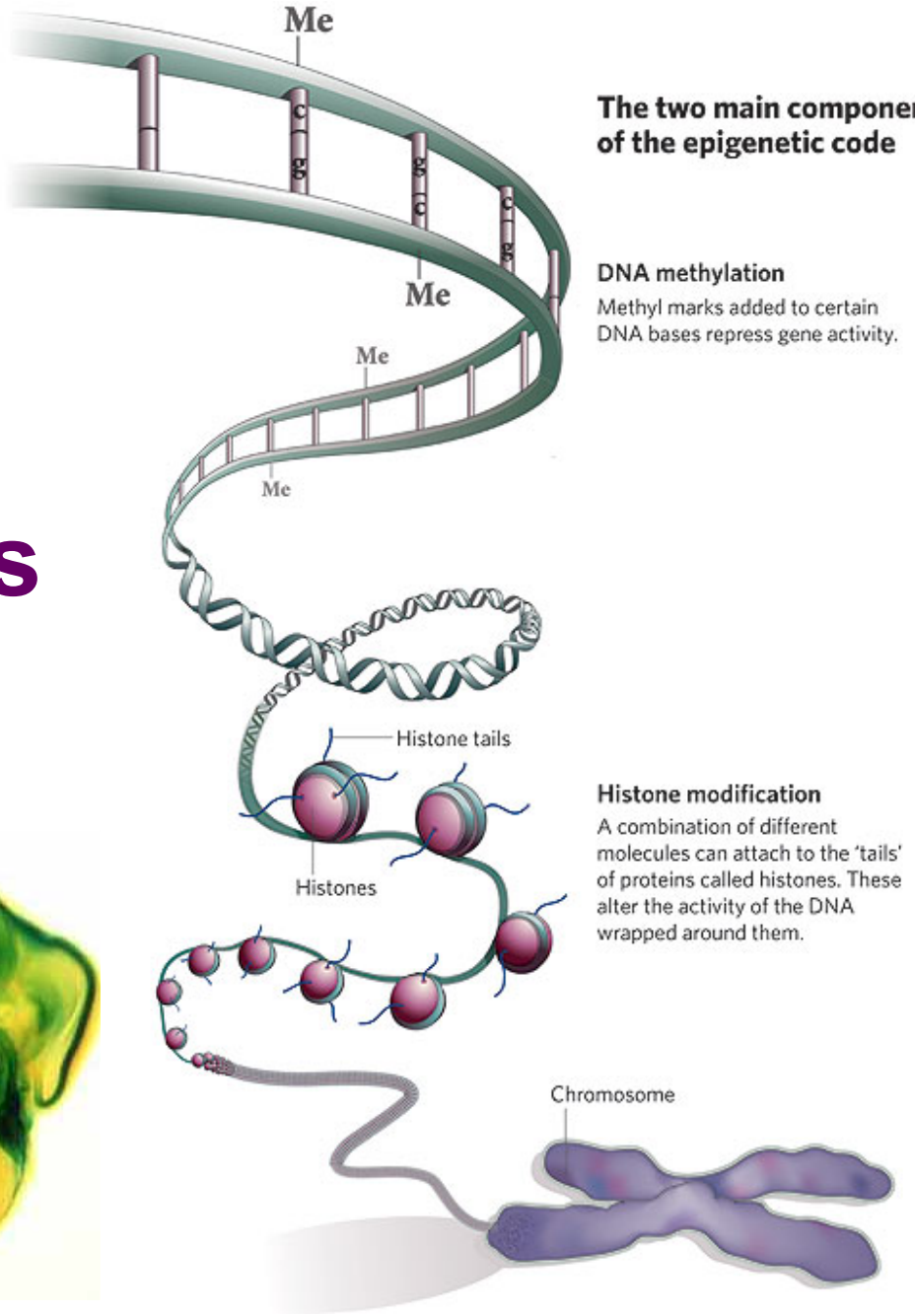
Chapter 19.2

Control of Eukaryotic Genes



The two main components of the epigenetic code

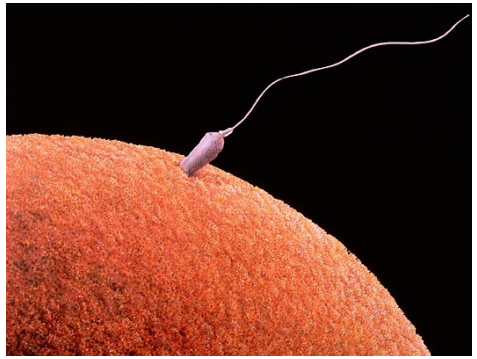
DNA methylation
Methyl marks added to certain DNA bases repress gene activity.

Histone modification
A combination of different molecules can attach to the 'tails' of proteins called histones. These alter the activity of the DNA wrapped around them.

How can cells have the same DNA but different sets of proteins?

- Genes are regulated independently of one another.
- In a given cell, the expression of some genes is “on” while other genes are “off”. Different cells express different sets of genes at different times.

The BIG Questions…



- How are genes turned on & off in eukaryotes?
- How do cells with the same genes differentiate to perform completely different, specialized functions?

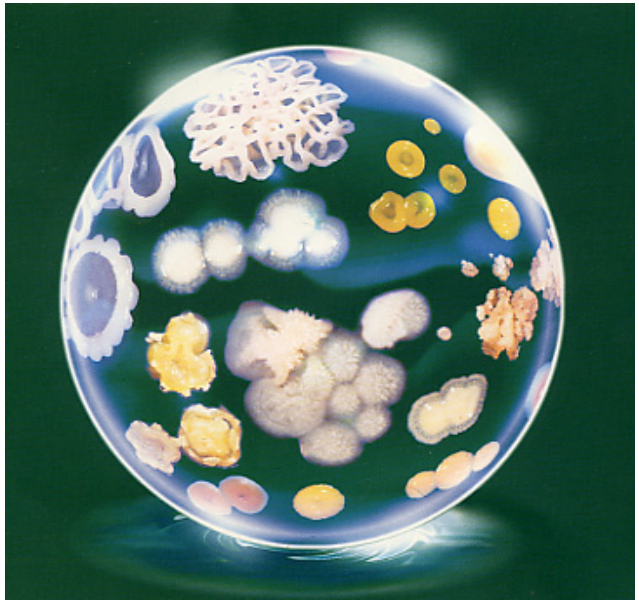
(a) 5 weeks.

(b) 14 weeks.

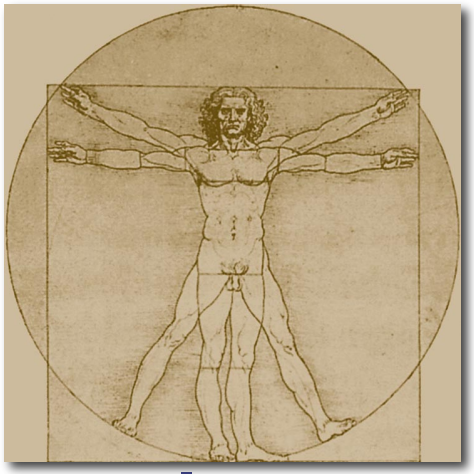
(c) 20 weeks.

Evolution of gene regulation

- **Prokaryotes**
  - single-celled
  - evolved to grow & divide rapidly
  - must respond quickly to changes in external environment
    - exploit transient resources
- **Gene regulation**
  - turn genes on & off rapidly
    - flexibility & reversibility
  - adjust levels of enzymes for synthesis & digestion



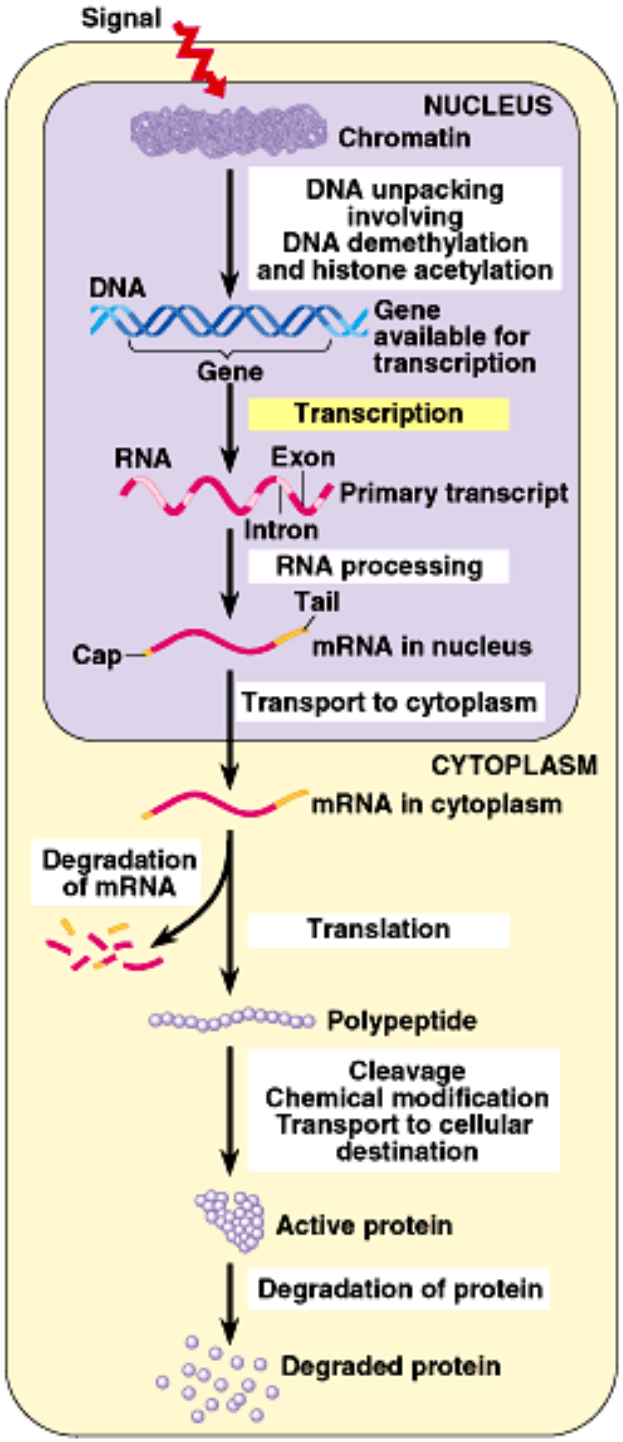
Evolution of gene regulation



- Eukaryotes
  - multicellular
  - evolved to maintain constant internal conditions while facing changing external conditions
    - homeostasis
  - regulate body as a whole
    - growth & development
      - long term processes
    - specialization
      - turn on & off large number of genes
    - must coordinate the body as a whole rather than serve the needs of individual cells

Points of control

- The control of gene expression can occur at any step in the pathway from gene to functional protein
  1. packing/unpacking DNA
  2. transcription
  3. mRNA processing
  4. mRNA degredation
  5. translation
  6. protein processing
  7. protein degradation



How does each (#1-7) control gene expression?

(1 sentence description)

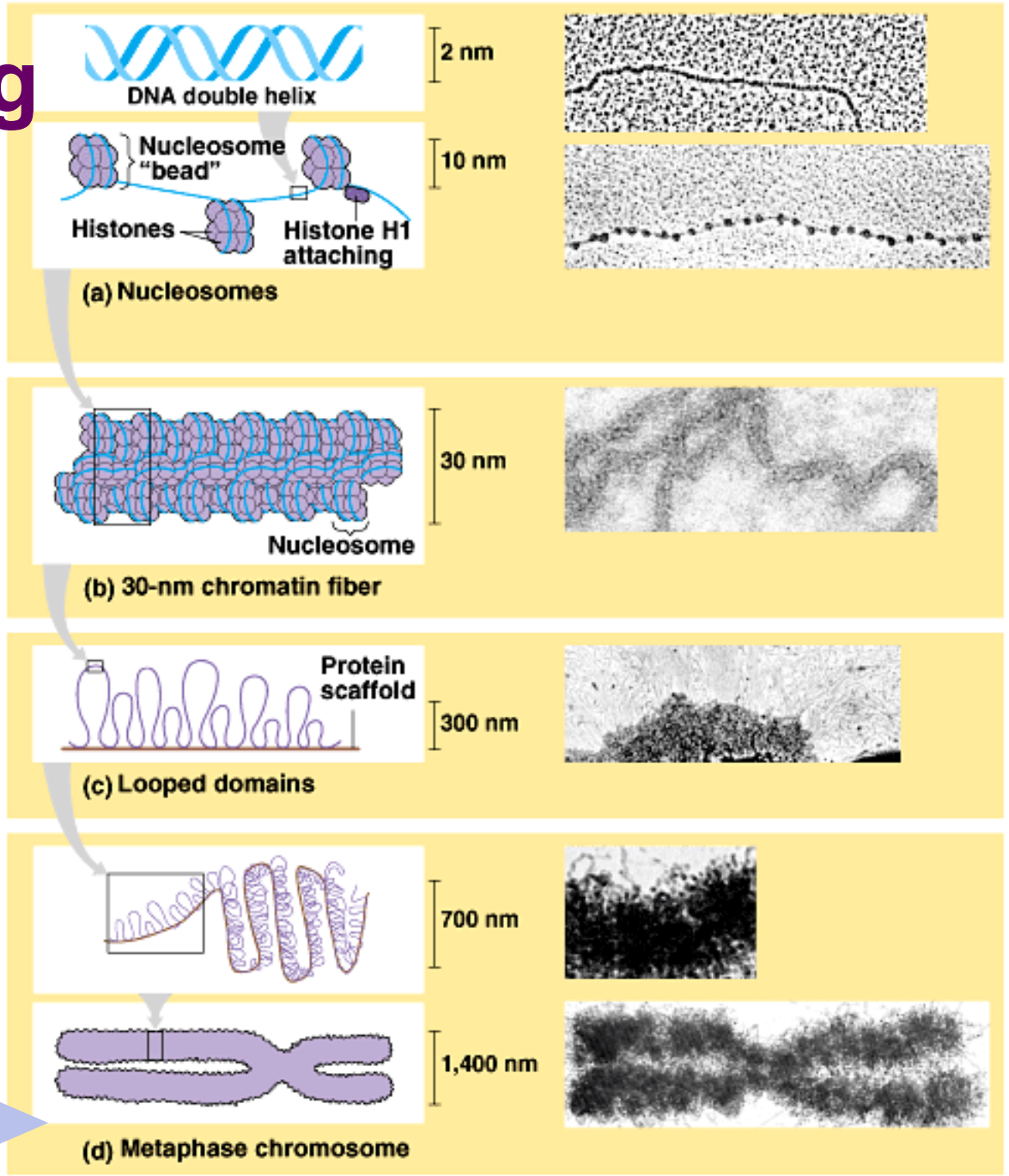
(Ex: #4 mRNA gets degraded faster if it's not needed. siRNA can silence genes (meaning it turns genes off).)

1. DNA packing

How do you fit all that DNA into nucleus?

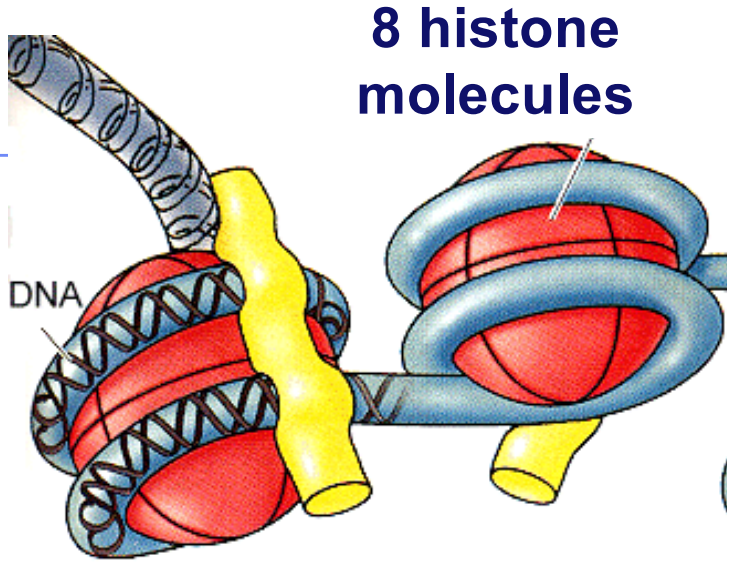
- DNA coiling & folding
  - double helix
  - nucleosomes
  - chromatin fiber
  - looped domains
  - chromosome

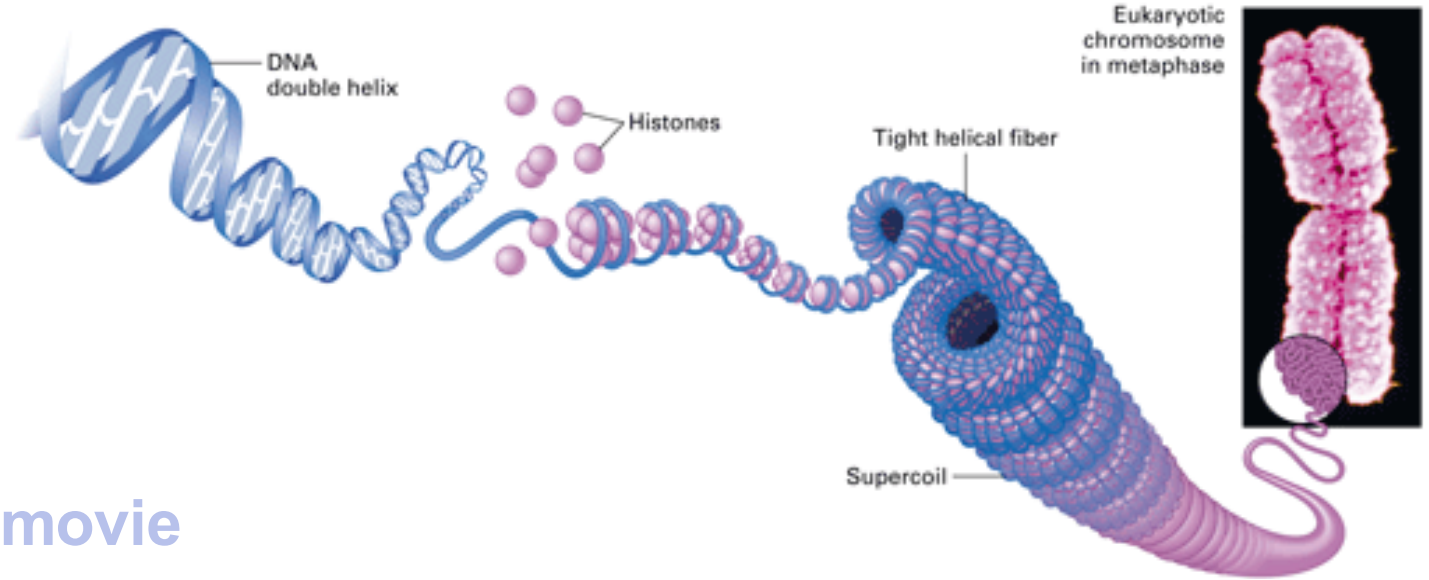
from DNA double helix to condensed chromosome



Nucleosomes

- "Beads on a string"
  - 1st level of DNA packing
  - histone proteins
    - 8 protein molecules
    - positively charged amino acids
    - bind tightly to negatively charged DNA



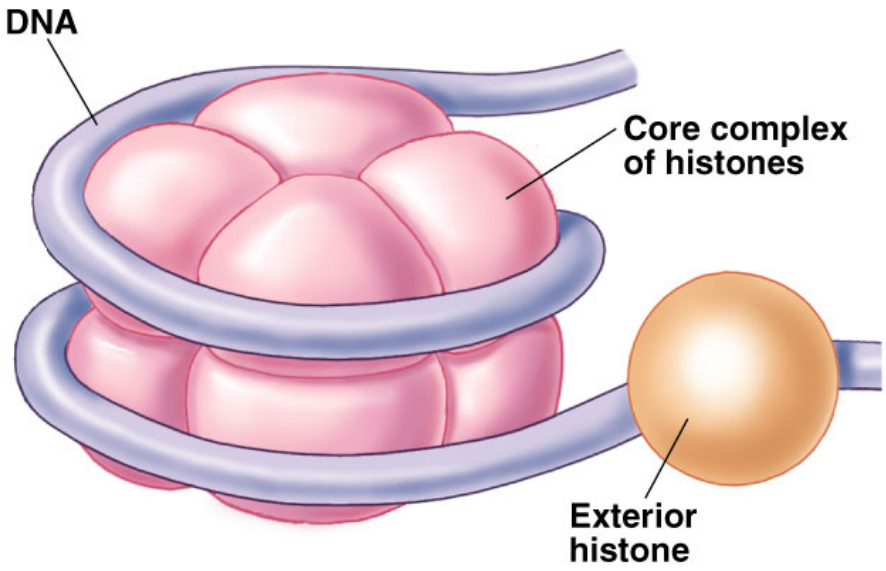


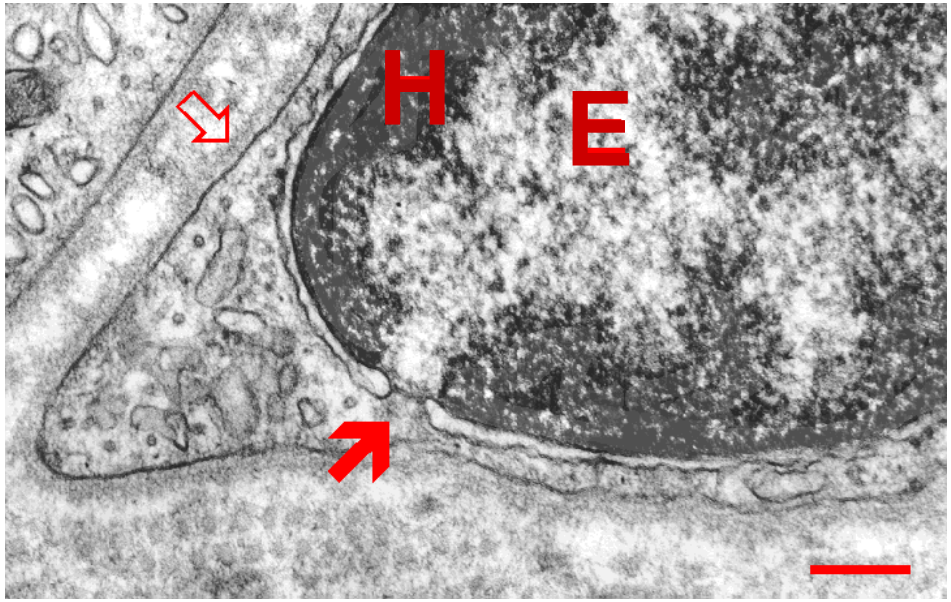
DNA packing movie

DNA packing as gene control

- **Degree of packing of DNA regulates transcription**
  - **tightly wrapped around histones**
    - **no transcription**
    - **genes turned off**

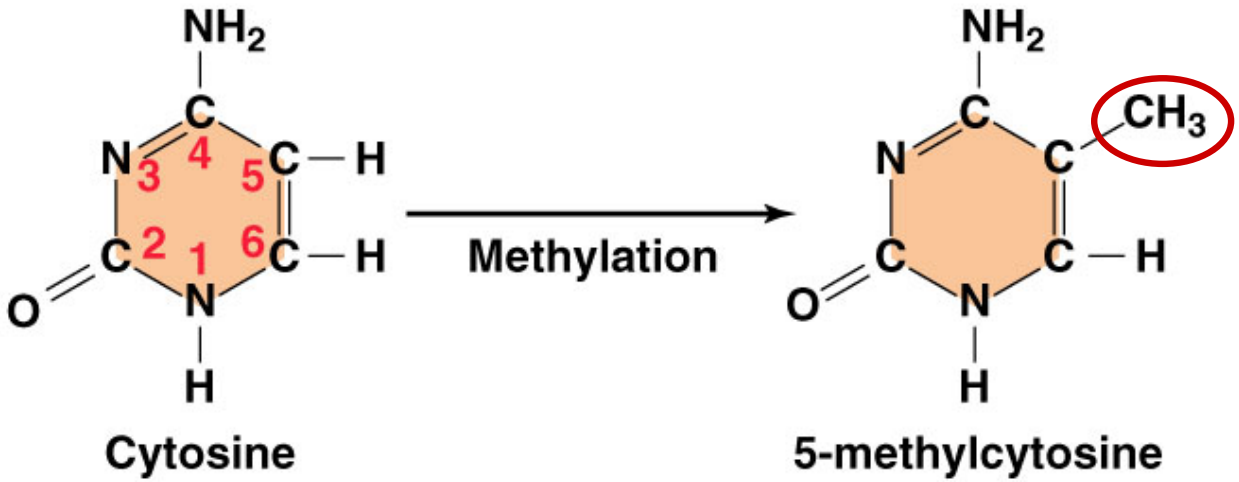
- **heterochromatin**
  darker DNA (H) = tightly packed
- **euchromatin**
  lighter DNA (E) = loosely packed





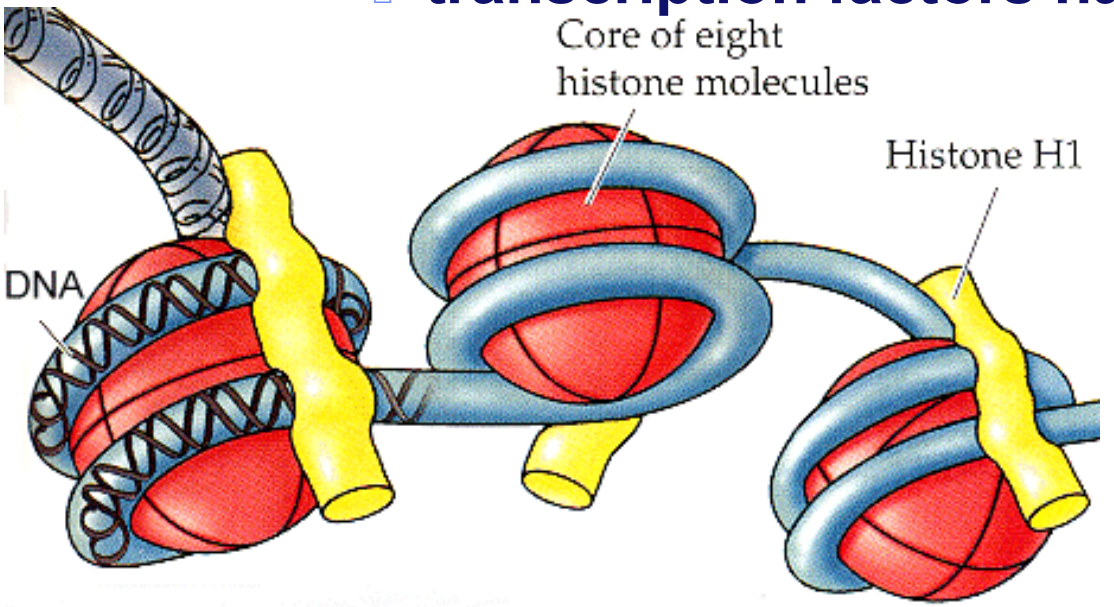
DNA methylation

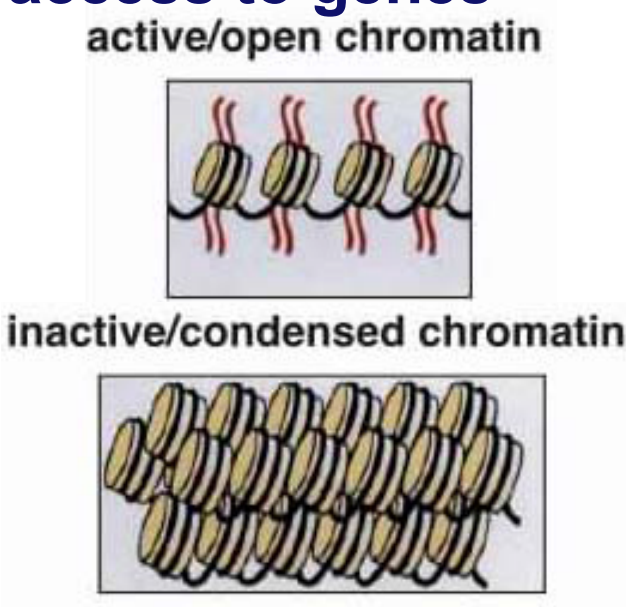
- **Methylation of DNA blocks transcription factors**
  - no transcription
    - → **genes turned off**
  - attachment of methyl groups ($-CH_3$) to cytosine
    - C = cytosine
  - nearly permanent inactivation of genes
    - ex. inactivated mammalian X chromosome = Barr body

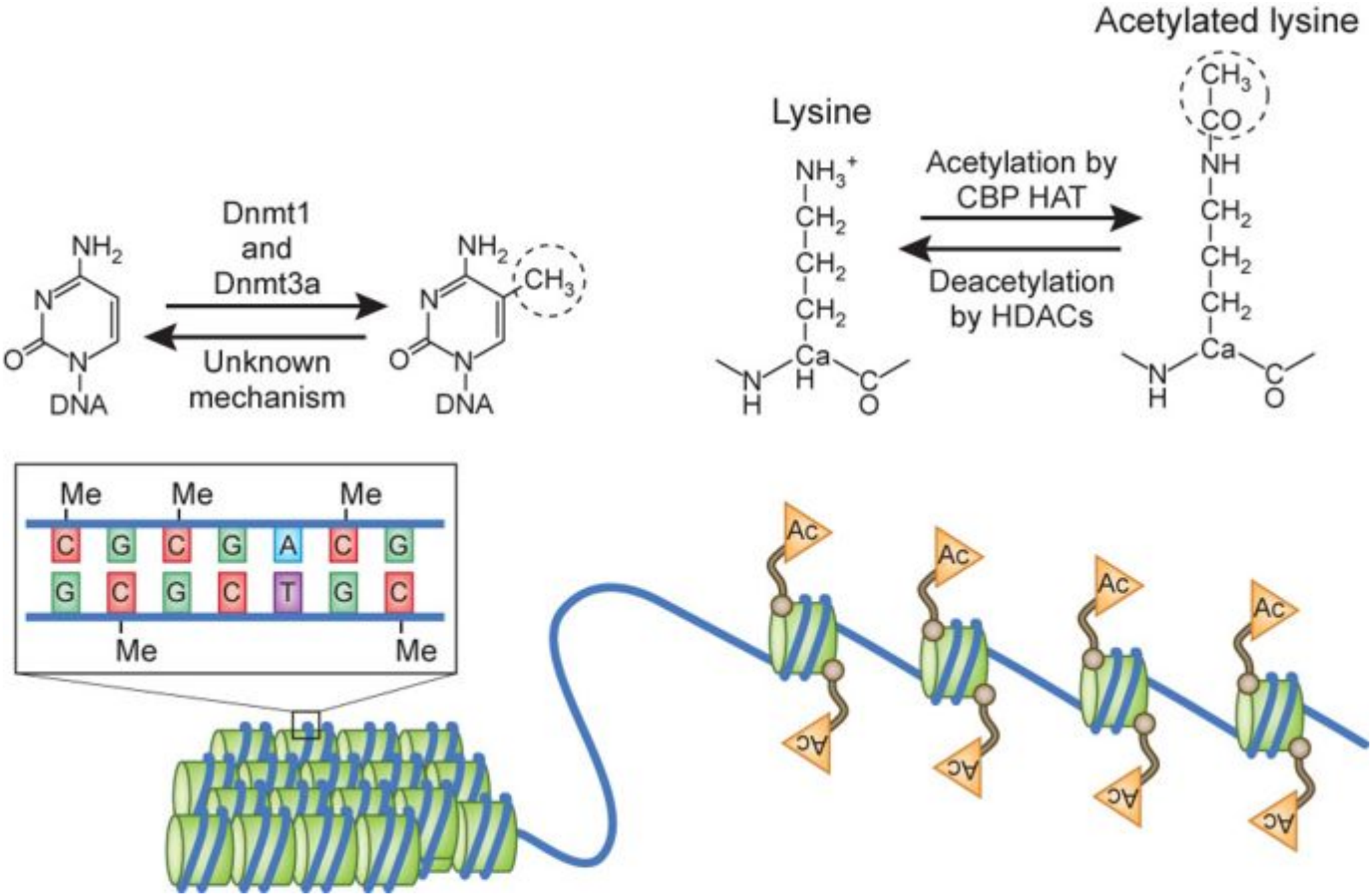


Histone acetylation

- **Acetylation of histones unwinds DNA**
  - **loosely wrapped around histones**
    - **enables transcription**
    - **genes turned on**
  - **attachment of acetyl groups ($-COCH_3$) to histones**
    - **conformational change in histone proteins**
    - **transcription factors have easier access to genes**

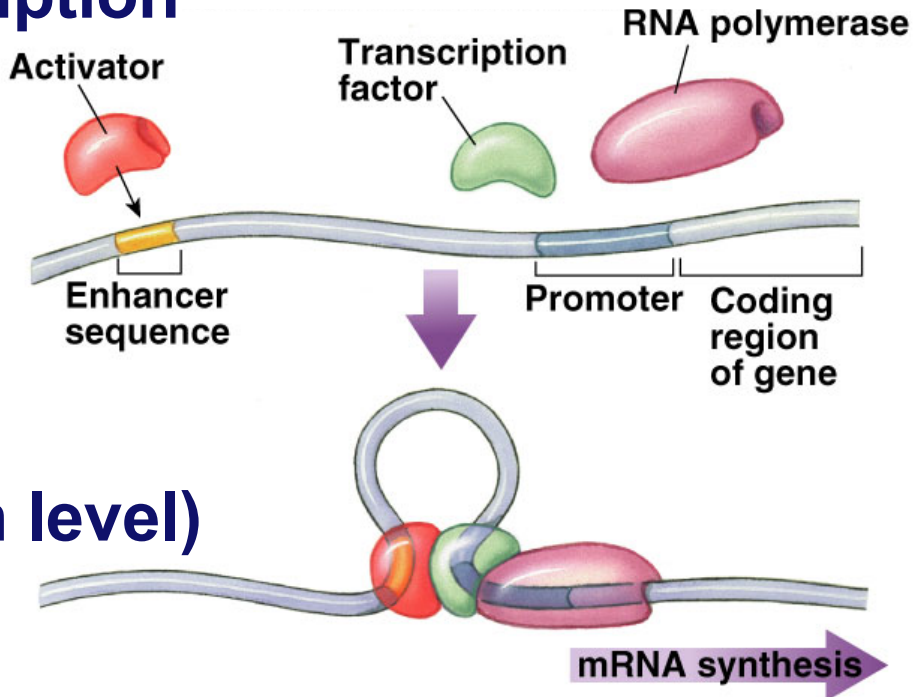




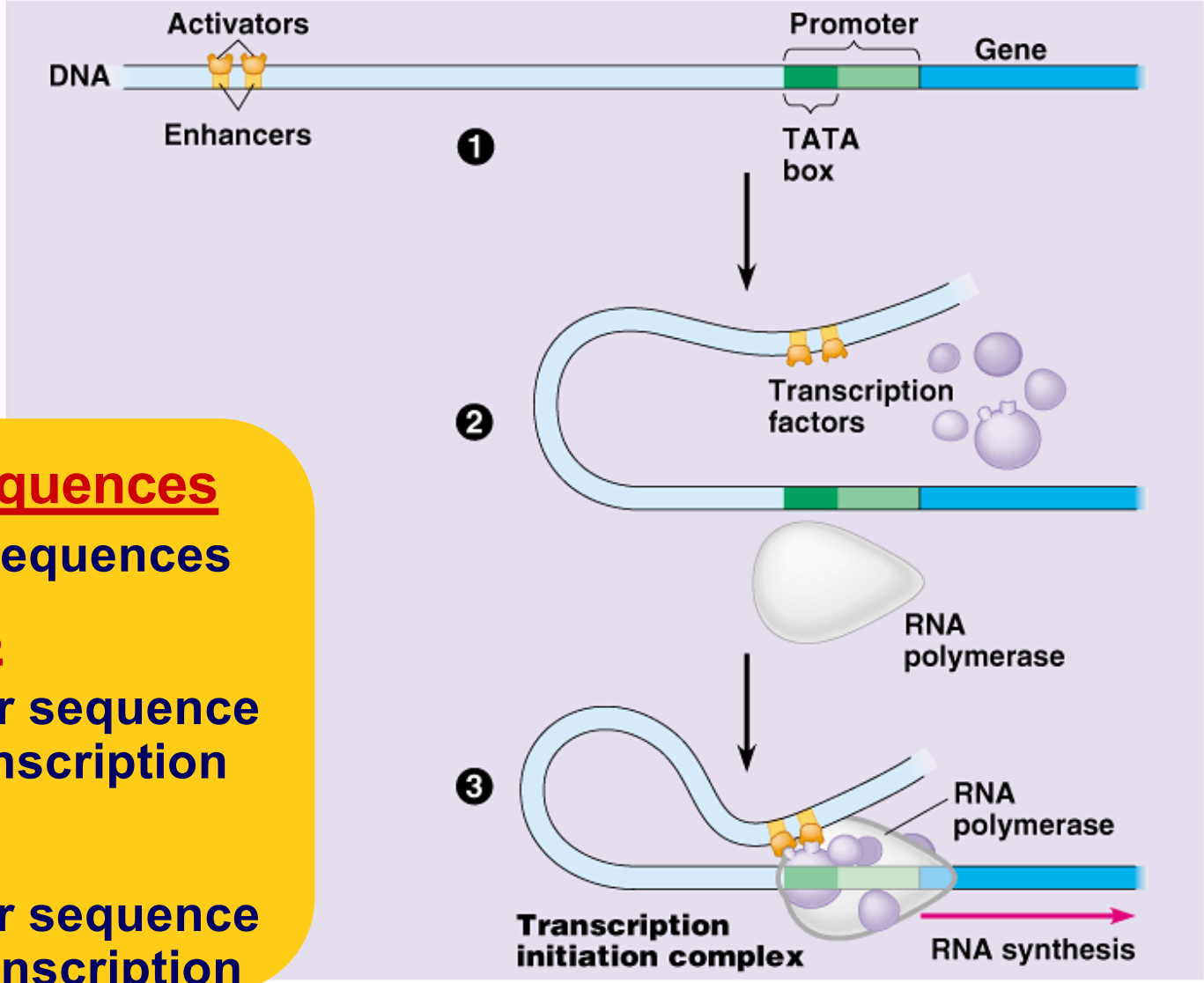

Acetylated lysine
Lysine
Acetylation by
CBP HAT
Deacetylation
by HDACs
Dnmt1
and
Dnmt3a
Unknown
mechanism
DNA
DNA
Me
Me
Me
Me
Me
C G C G A C G
G C G C T G C
Ac

2. Transcription initiation

- Control regions on DNA
  - promoter
    - nearby control sequence on DNA
    - binding of RNA polymerase & transcription factors
    - "base" rate of transcription
  - enhancer
    - distant control sequences on DNA
    - binding of activator proteins
    - "enhanced" rate (high level) of transcription



Model for Enhancer action

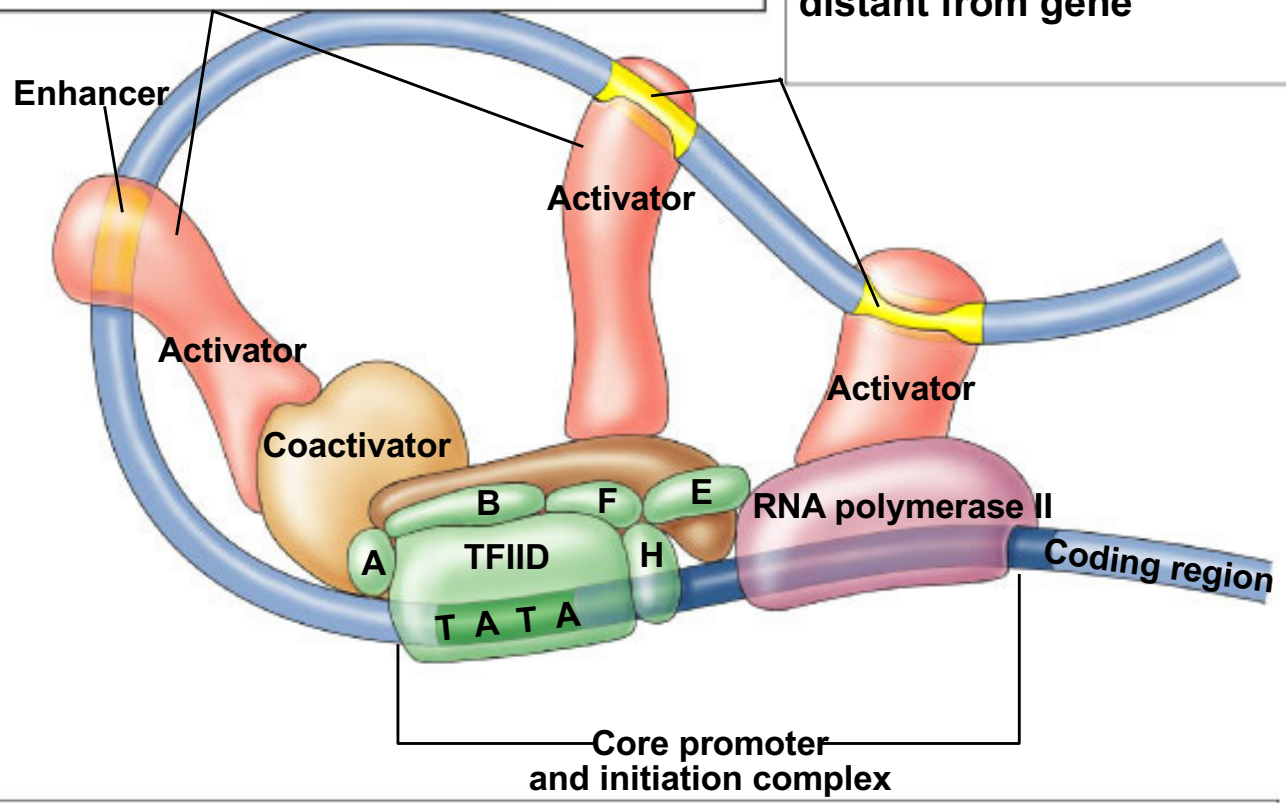


- **Enhancer DNA sequences**
  - distant control sequences
- **Activator proteins**
  - bind to enhancer sequence & stimulates transcription
- **Silencer proteins**
  - bind to enhancer sequence & block gene transcription

Transcription complex

Activator Proteins
- regulatory proteins bind to DNA at distant enhancer sites
- increase the rate of transcription

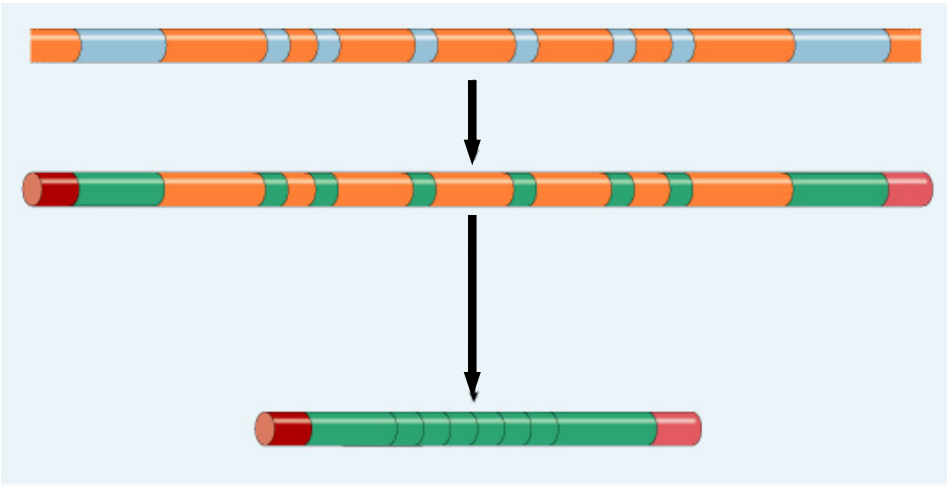
Enhancer Sites
regulatory sites on DNA distant from gene

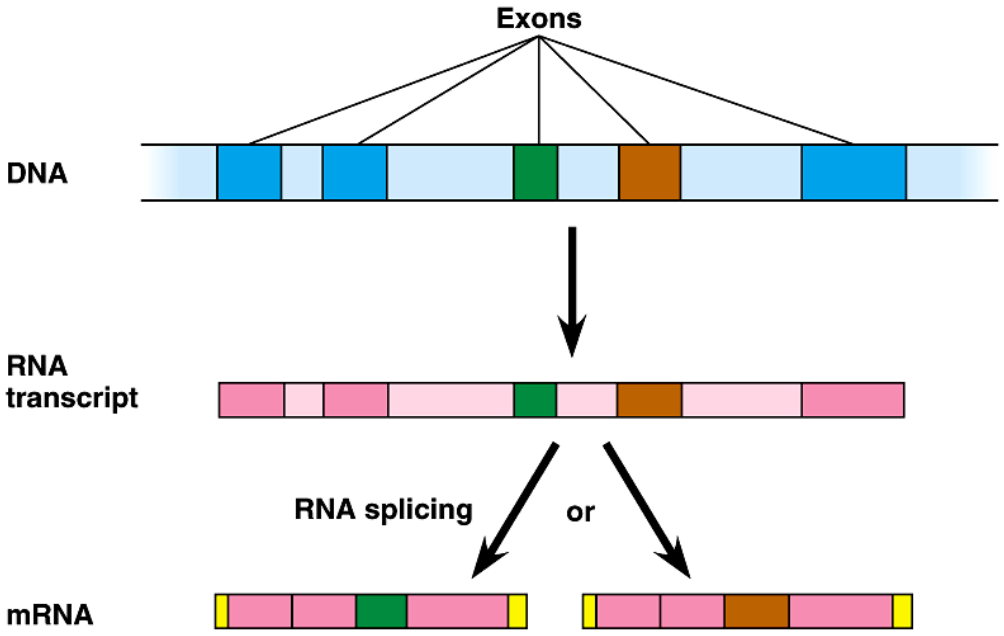


Initiation Complex at Promoter Site binding site of RNA polymerase

3. mRNA processing (Post-transcriptional control)

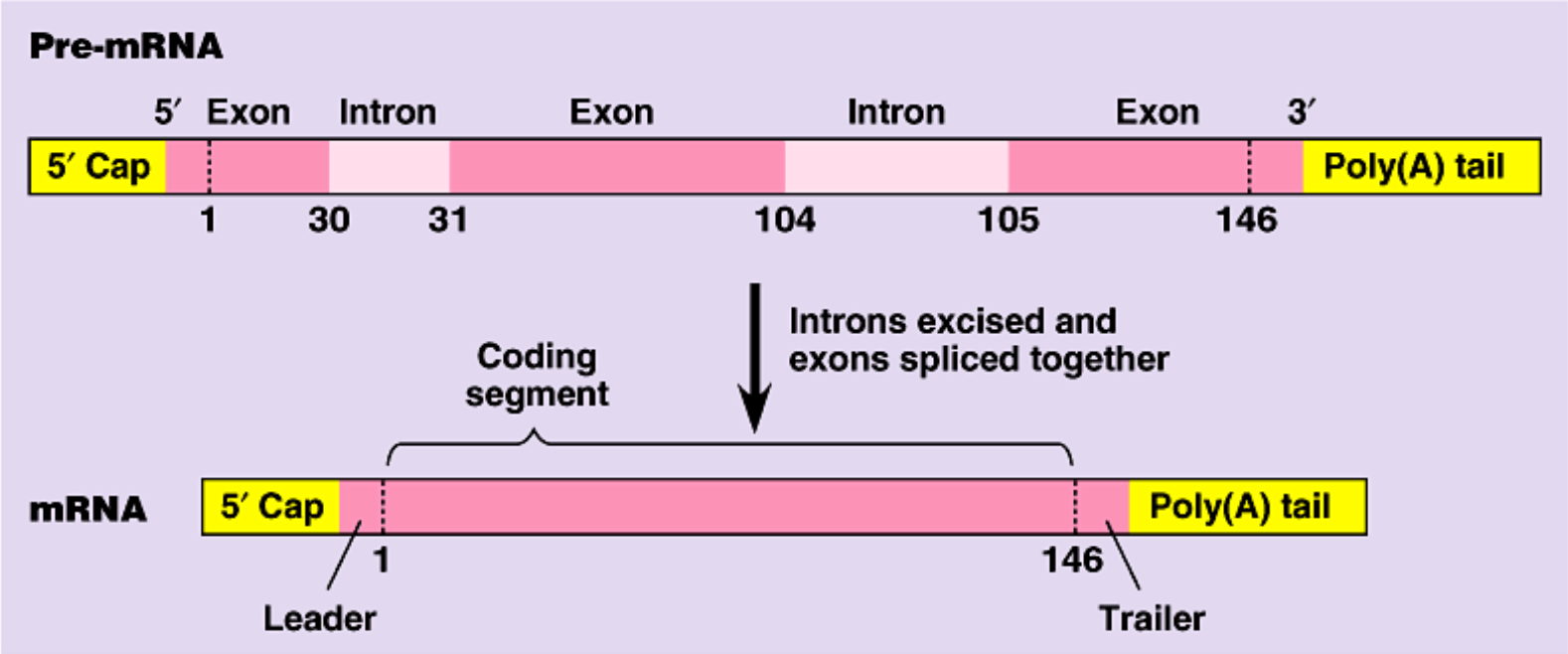
- Alternative RNA splicing
  - variable processing of exons creates a family of proteins





4. Regulation of mRNA degradation

- **Life span of mRNA determines amount of protein synthesis**
  - **mRNA can last from hours to weeks**

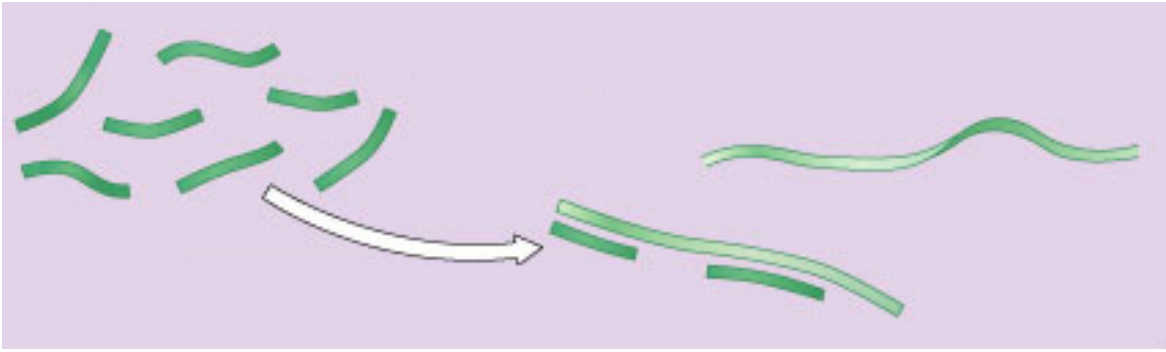


RNA processing movie

RNA interference

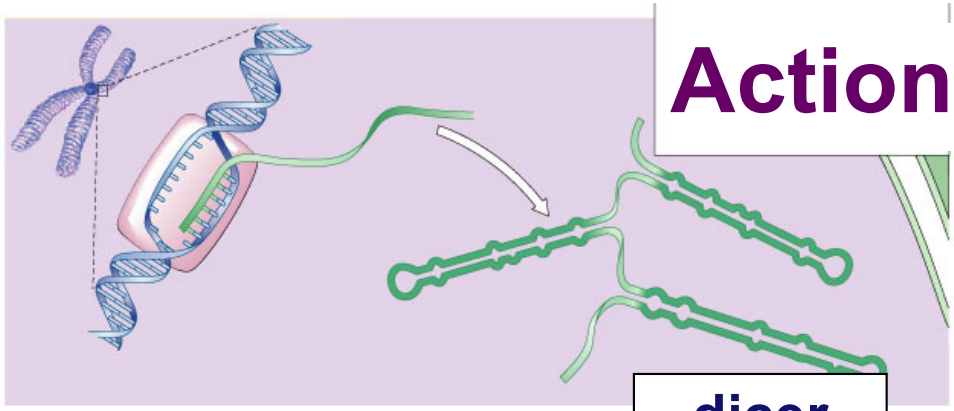
- **Small interfering RNAs (siRNA)**
  - short segments of RNA (21-28 bases)
    - bind to mRNA
    - create sections of double-stranded mRNA
    - "death" tag for mRNA
      - triggers degradation of mRNA
  - cause gene "silencing"
    - post-transcriptional control
    - turns off gene = no protein produced

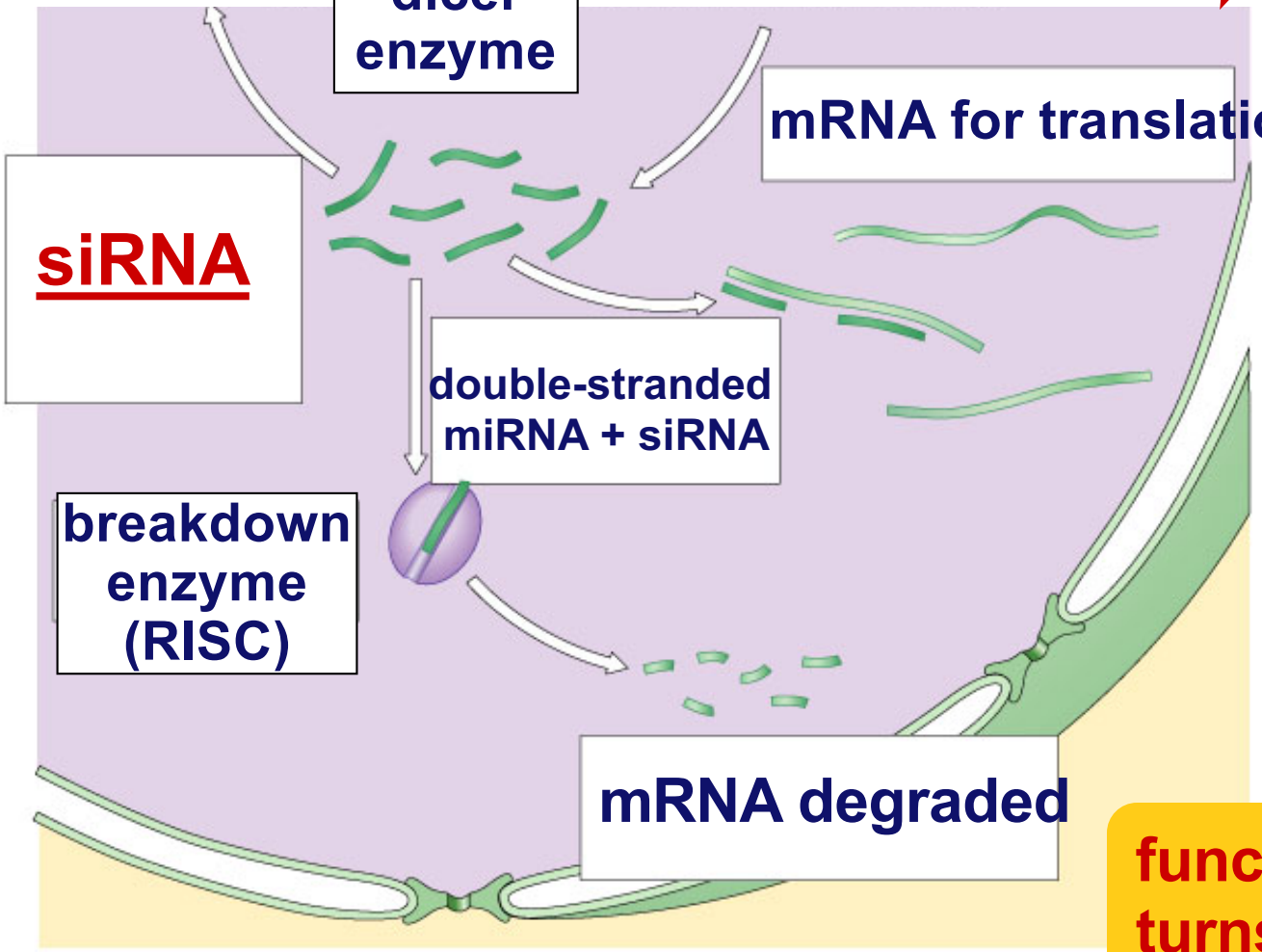
siRNA



Action of siRNA

Hot...Hot new topic in biology

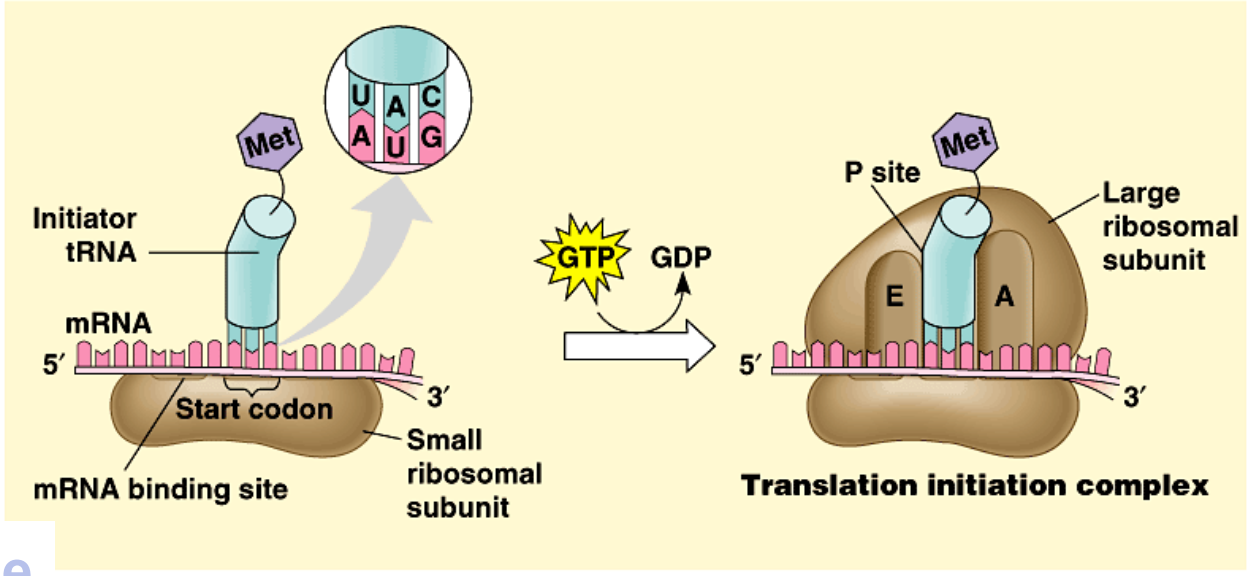




functionally turns gene off

5. Control of translation

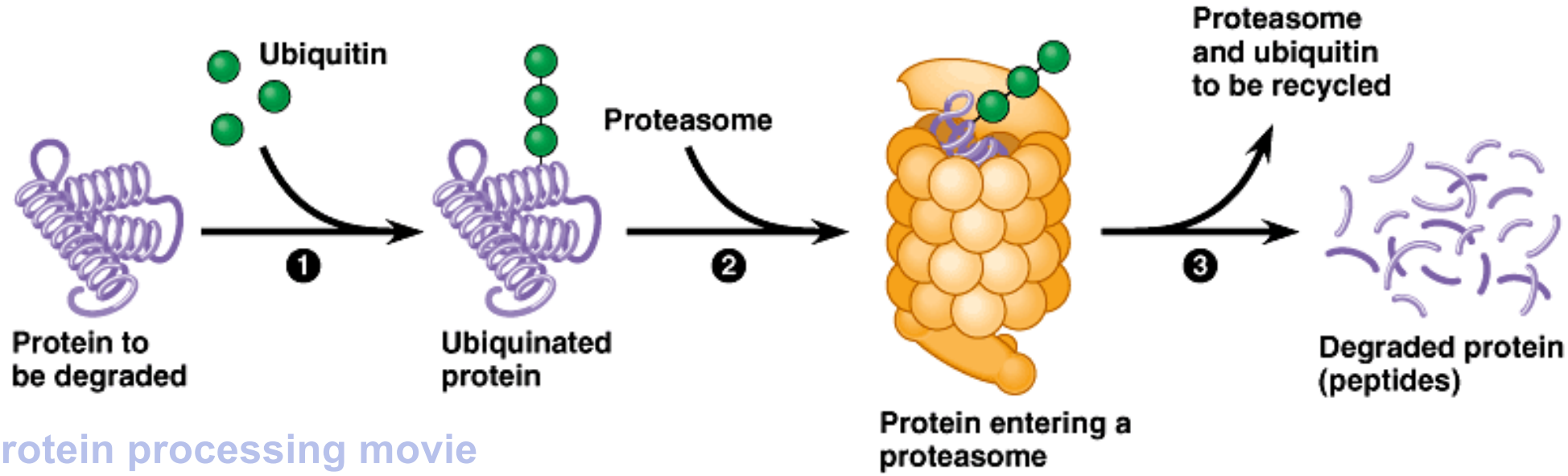
- **Block initiation of translation stage**
  - **regulatory proteins attach to 5' end of mRNA**
    - **prevent attachment of ribosomal subunits & initiator tRNA**
    - **block translation of mRNA to protein**



Control of translation movie

6-7. Protein processing & degradation

- **Protein processing**
  - folding, cleaving, adding sugar groups, targeting for transport
- **Protein degradation**
  - **ubiquitin** tagging
  - **proteasome** degradation

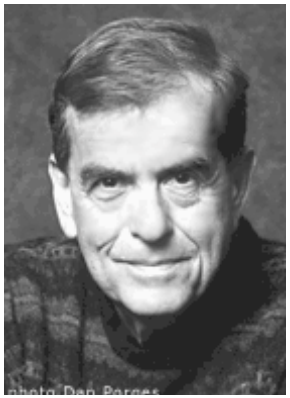


Protein processing movie

1980s | 2004

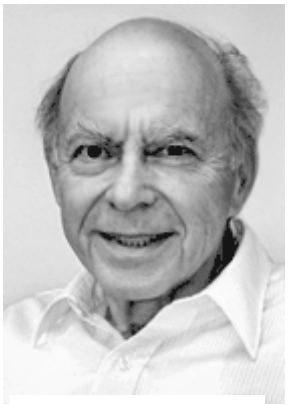
Ubiquitin

- "Death tag"
  - mark unwanted proteins with a label
  - 76 amino acid polypeptide, ubiquitin
  - labeled proteins are broken down rapidly in "waste disposers"
    - proteasomes



Aaron Ciechanover
Israel

Avram Hershko
Israel



Irwin Rose
UC Riverside

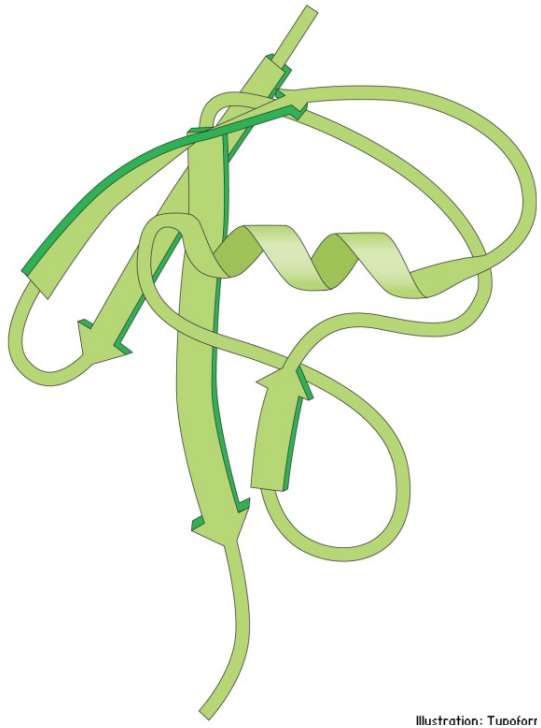
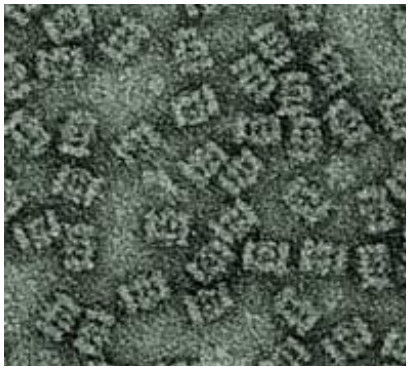
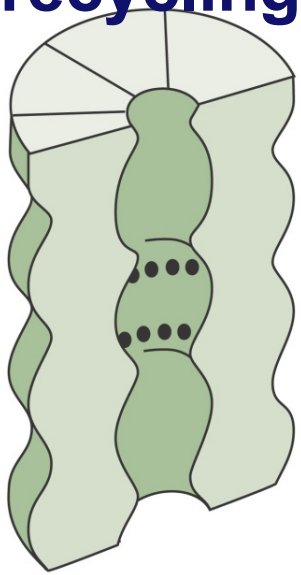


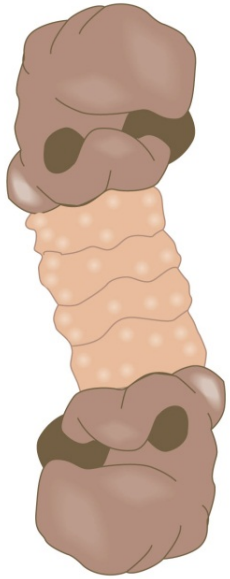
Illustration: Typoforr

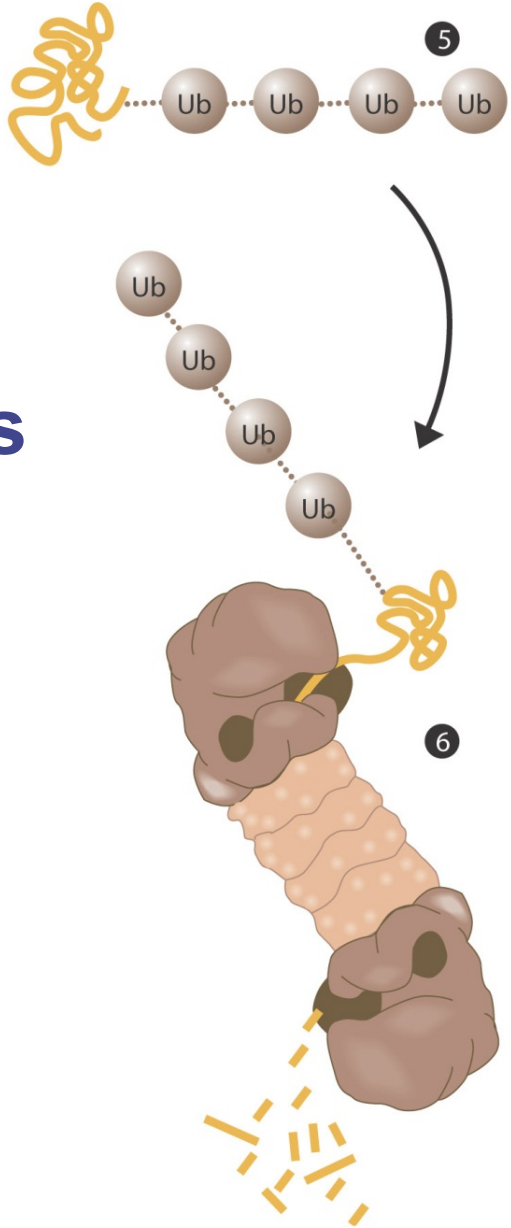
Proteasome

- **Protein-degrading "machine"**
  - **cell's waste disposer**
  - **breaks down any proteins into 7-9 amino acid fragments**
    - **cellular recycling**



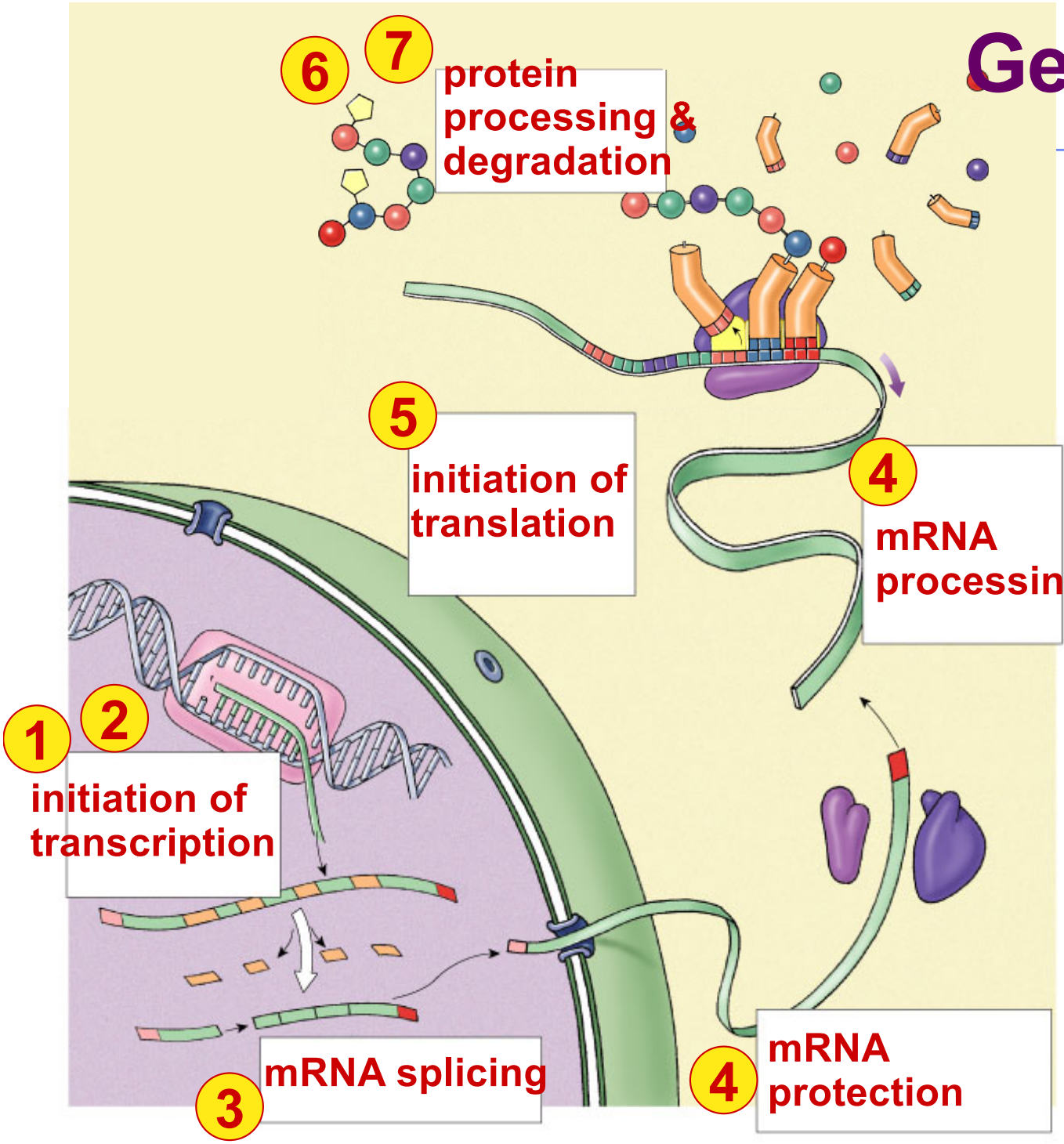






play Nobel animation

Gene Regulation



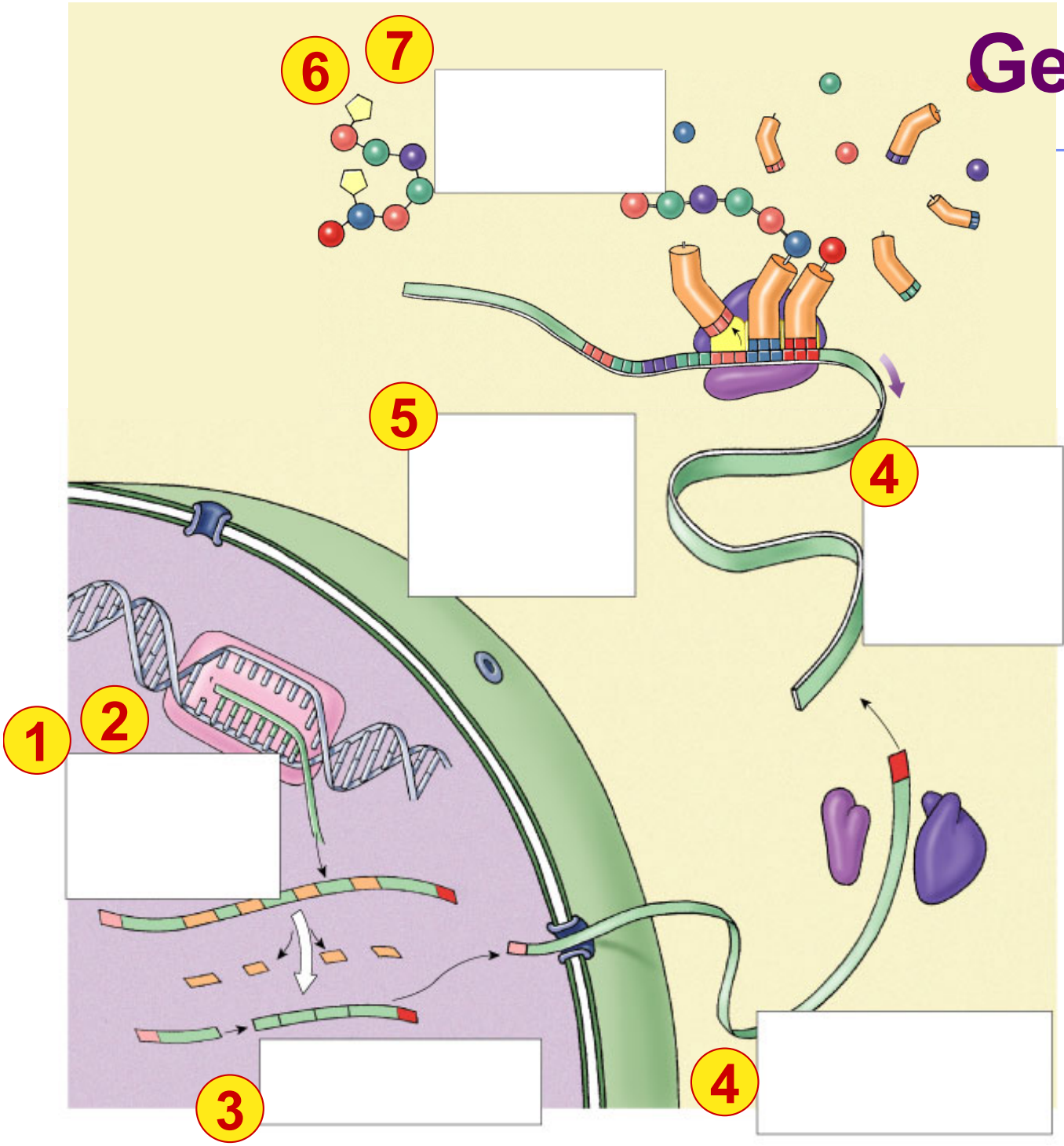
1 & 2. transcription
- DNA packing
- transcription factors

3 & 4. post-transcription
- mRNA processing
- splicing
- 5' cap & poly-A tail
- breakdown by siRNA

5. translation
- block start of translation

6 & 7. post-translation
- protein processing
- protein degradation

Gene Regulation



1 & 2. _____

- _____
- _____

3 & 4. _____

- _____
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6 & 7. _____

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