Gene Regulation Overview

Transcriptional Control

- Promoter accessibility
- Transcription factor binding
- RNA polymerase recruitment
- Primary regulation point

Enhancers and Silencers

- Regulatory DNA sequences
- Can be far from gene
- Increase or decrease transcription
- Bind transcription factors

Chromatin Remodeling

- ATP-dependent complexes
- Alter nucleosome positioning
- Expose or hide DNA
- Control gene accessibility

Post-transcriptional

- mRNA stability regulation
- Alternative splicing
- MicroRNA regulation
- Translation control

1 Transcriptional Control

Transcriptional control is the primary mechanism for regulating gene expression, determining whether a gene is turned on or off at the level of RNA synthesis.

Transcription Initiation Complex

Key Components:

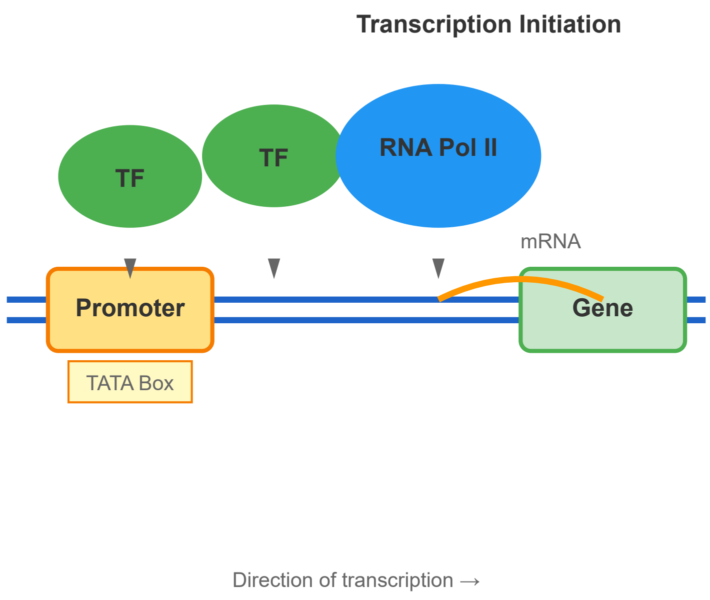
- **Promoter Region:** DNA sequence where RNA polymerase binds to initiate transcription. Contains core elements like TATA box and CAAT box.
- **Transcription Factors (TFs):** Proteins that bind to specific DNA sequences to activate or repress transcription.
- **RNA Polymerase II:** The enzyme complex that synthesizes mRNA from the DNA template.
- **Mediator Complex:** Bridges transcription factors and RNA polymerase, essential for transcription initiation.

Mechanism:

When a cell needs to express a gene, specific transcription factors bind to the promoter and enhancer regions. This recruitment facilitates the assembly of the pre-initiation complex, including RNA polymerase II. The polymerase then unwinds the DNA double helix and begins synthesizing mRNA.

Example:

The lac operon in bacteria demonstrates transcriptional control, where lactose presence induces transcription of genes needed for lactose metabolism.



2 Enhancers and Silencers

Enhancers and silencers are regulatory DNA sequences that control gene expression from a distance, sometimes located thousands of base pairs away from the genes they regulate.

Enhancers:

- **Function:** Increase transcription rate by recruiting activator proteins and transcriptional machinery.
- **Location:** Can be upstream, downstream, or within introns of target genes.
- **Orientation Independent:** Work regardless of their orientation relative to the promoter.
- **Distance Independent:** Can function from great distances through DNA looping.

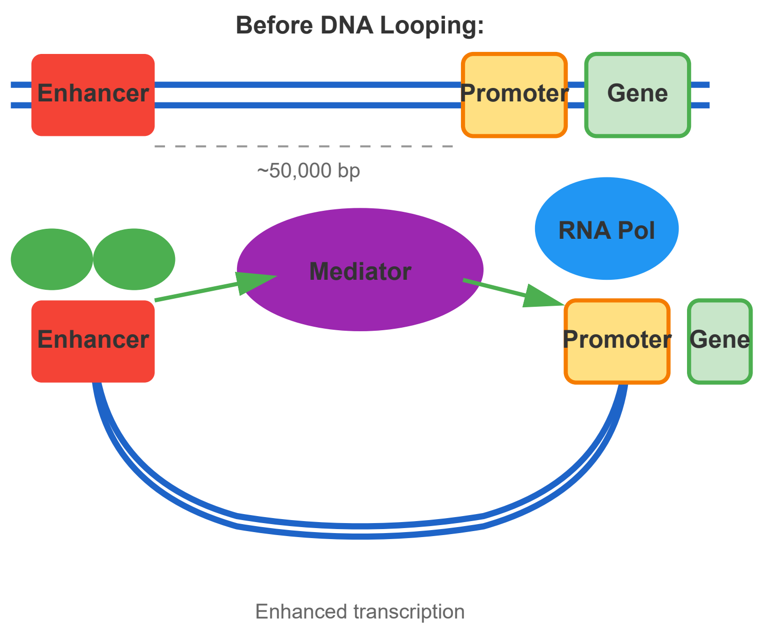
Silencers:

- **Function:** Decrease or block transcription by recruiting repressor proteins.
- **Mechanism:** Can interfere with activator binding or recruit chromatin-modifying enzymes that compact DNA.

DNA Looping:

The Mediator complex and cohesin proteins facilitate DNA looping, bringing distant enhancers into close proximity with promoters. This creates a three-dimensional structure that enables long-range gene regulation.

Enhancer-Promoter Interaction via DNA Looping

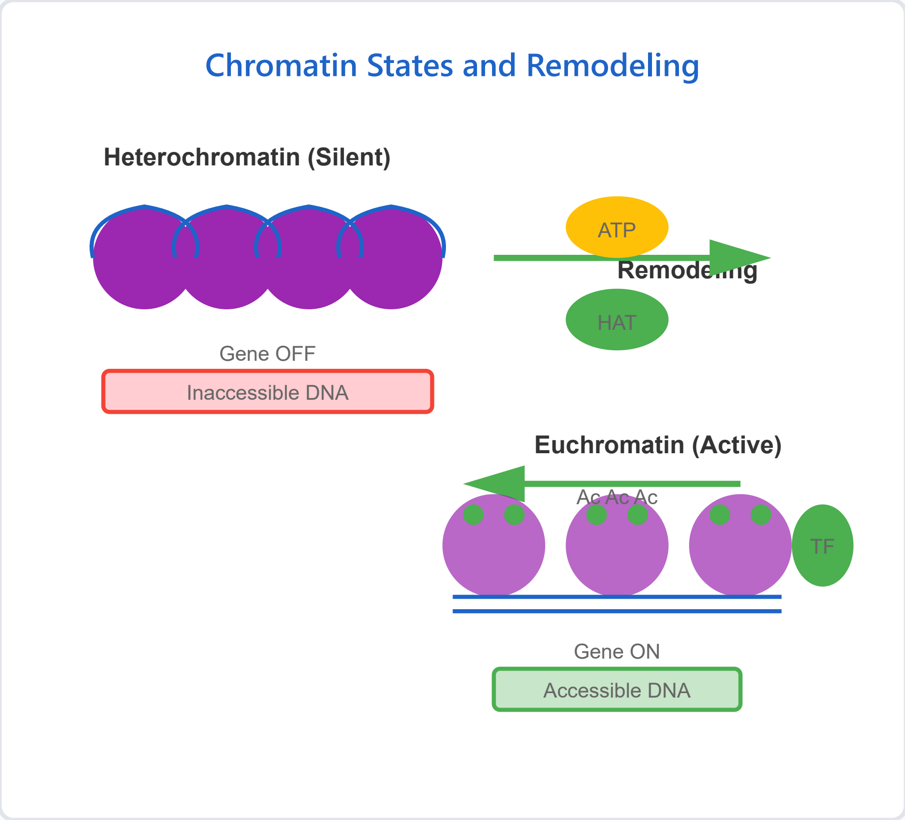


Example:

The β-globin locus control region (LCR) is located 50 kb upstream of the β-globin gene but is essential for high-level expression in red blood cells.

3 Chromatin Remodeling

Chromatin remodeling involves the dynamic modification of chromatin structure to regulate DNA accessibility for transcription, replication, and repair.



Chromatin Structure:

- **Nucleosome:** Basic unit consisting of DNA wrapped around histone octamer (2 copies each of H2A, H2B, H3, H4).
- **Euchromatin:** Loosely packed, transcriptionally active chromatin.
- **Heterochromatin:** Tightly packed, transcriptionally silent chromatin.

Remodeling Mechanisms:

- **ATP-dependent Remodeling:** Complexes like SWI/SNF, ISWI, and CHD use ATP hydrolysis to slide, eject, or restructure nucleosomes.

- **Histone Modifications:** Acetylation (activation), methylation (activation or repression), phosphorylation, and ubiquitination alter chromatin structure.
- **Histone Variant Exchange:** Replacement of canonical histones with variants (e.g., H2A.Z, H3.3) affects nucleosome stability.

Histone Acetylation:

Histone acetyltransferases (HATs) add acetyl groups to lysine residues, neutralizing positive charges and loosening DNA-histone interactions. This makes DNA more accessible for transcription. Conversely, histone deacetylases (HDACs) remove acetyl groups, promoting gene silencing.

Example:

During development, chromatin remodeling enables cell differentiation by making lineage-specific genes accessible while silencing others.

4 Post-transcriptional Regulation

Post-transcriptional regulation controls gene expression after mRNA synthesis, providing additional layers of control over protein production.

Post-transcriptional Regulation Mechanisms

mRNA Stability:

- **5' Cap and 3' Poly-A Tail:** Protect mRNA from degradation and enhance translation.
- **RNA-Binding Proteins:** Stabilize or destabilize mRNA by binding to regulatory sequences in UTRs.
- **Deadenylation:** Removal of poly-A tail triggers mRNA decay.

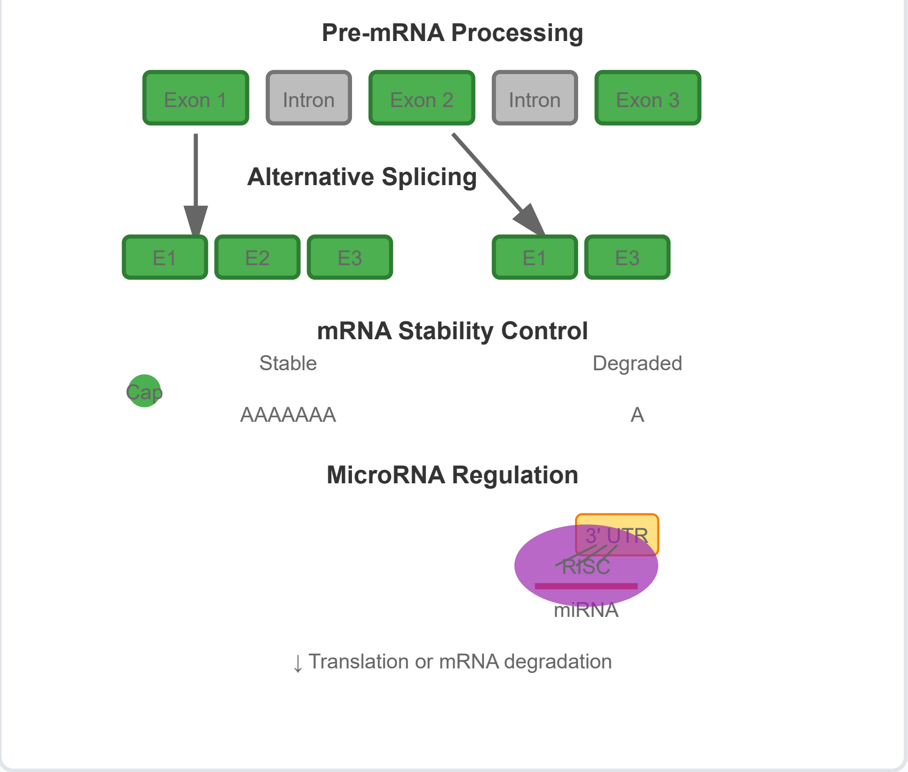
Alternative Splicing:

- **Mechanism:** Different combinations of exons are joined together, producing multiple protein isoforms from a single gene.
- **Regulation:** SR proteins (serine/arginine-rich) promote exon inclusion, while hnRNPs promote exon skipping.
- **Impact:** Over 95% of human multi-exon genes undergo alternative splicing, greatly expanding protein diversity.

MicroRNA Regulation:

- **Biogenesis:** miRNAs are ~22 nucleotide RNAs processed from longer precursors.
- **Mechanism:** miRNAs bind to complementary sequences in target mRNA 3' UTRs, leading to translational repression or mRNA degradation.
- **RISC Complex:** miRNA-loaded RNA-induced silencing complex mediates gene silencing.

Translation Control:



Regulatory proteins and upstream open reading frames (uORFs) in 5' UTRs can modulate ribosome binding and scanning, controlling translation initiation efficiency.

Example:

The Dscam gene in Drosophila produces over 38,000 different protein isoforms through alternative splicing, crucial for neural wiring specificity.