D1.2 Protein Synthesis (HL)

Transcription: Synthesis of RNA using a DNA template

Transcription is required for the expression of genes.

Steps of Transcription:

1. RNA polymerase binds to the DNA and unwinds the double helix
2. RNA polymerase moves along the template strand, reading the base sequence
3. Free RNA nucleotides pair with exposed DNA template bases by complementary base pairing (DNA A pairs with RNA U; DNA T pairs with RNA A; C pairs with G), held in place by hydrogen bonds
4. RNA polymerase joins nucleotides by covalent bonds, forming a growing mRNA strand
5. mRNA is released when RNA polymerase reaches a termination sequence; DNA helix reforms

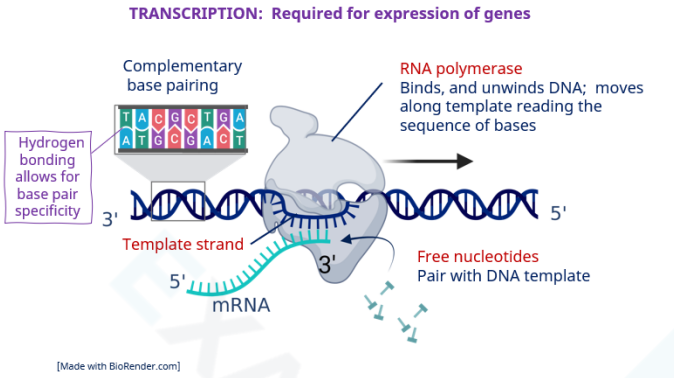


Figure 1. Transcription: RNA polymerase synthesises mRNA from the DNA template strand (5'→3').

Concept	Key Point
Hydrogen bonding	Complementary base pairing via H-bonds ensures accurate copying; DNA strands re-pair after RNA polymerase passes
DNA template stability	DNA sequence unchanged during transcription; helix reforms allowing repeated use. In somatic cells, the DNA sequence must be conserved throughout the life of the cell
Gene expression	Not all genes are transcribed at once; cells control which genes are active by regulating transcription (e.g. insulin gene only transcribed in pancreatic β cells)

Roles of mRNA, Ribosomes and tRNA

mRNA (messenger RNA):

- Carries coded sequence of codons from DNA to the ribosome
- Has a ribosome-binding site, a **start codon** (AUG) and **stop codons** (UAA, UAG, UGA)
- Binds to the **small subunit** of the ribosome

Ribosomes:

- Made of two subunits: small (mRNA binding) and large (tRNA binding + peptide bond formation)
- Two tRNA molecules typically bind simultaneously to the large subunit, at A and P sites

tRNA (transfer RNA):

- Cloverleaf-shaped; **anticodon** loop at one end, amino acid attachment site at 3' end
- Each tRNA is specific: a dedicated activating enzyme attaches the correct amino acid
- Complementary pairing of codon and anticodon ensures correct amino acid delivery

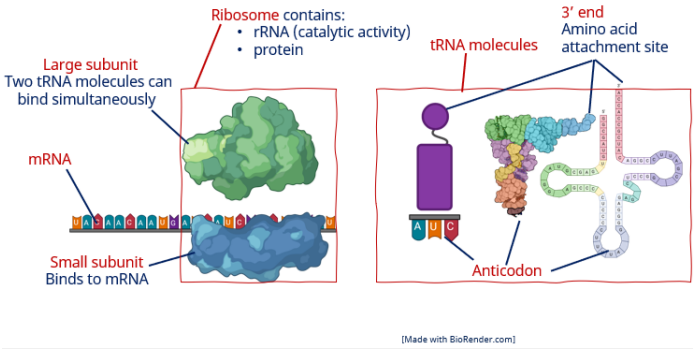


Figure 2. Structure and roles of mRNA, tRNA and ribosomes in translation.

Features of the Genetic Code

Feature	Explanation
Why triplet?	2-base code gives only 16 combinations; 3-base code gives 64 - enough for all 20 amino acids + start and stop signals
Degenerate	Most amino acids coded by more than one codon; reduces impact of mutations
Universal	Same codons used by virtually all organisms: evidence of common ancestry
Start codon	AUG (codes for methionine); signals start of translation
Stop codons	UAA, UAG, UGA do not code for amino acids; end translation

Translation: Stepwise Movement of the Ribosome

Translation is the synthesis of a polypeptide from an mRNA template. The base sequence of mRNA is decoded into the amino acid sequence of a polypeptide, occurring in the cytoplasm at ribosomes. Each cycle adds one amino acid to the growing polypeptide:

1. A tRNA carrying an amino acid binds to the ribosome; its anticodon pairs with the complementary mRNA codon
2. A second tRNA enters, carrying the next amino acid; anticodon pairs with next codon
3. A peptide bond forms between the two adjacent amino acids, extending the polypeptide
4. Ribosome translocates 3 bases (one codon) along mRNA; empty tRNA exits

Cycle repeats until a stop codon; polypeptide and tRNA released; ribosome dissociates.

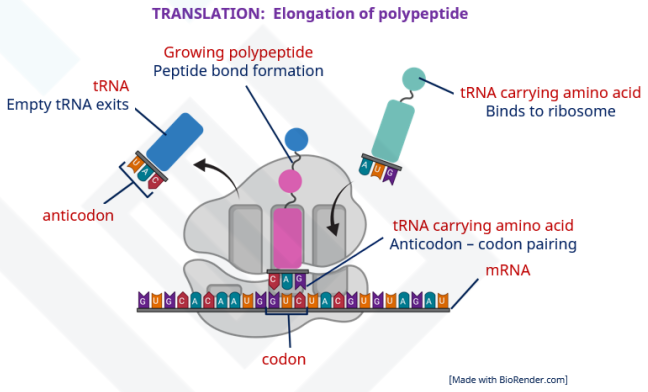


Figure 3. Translation: elongation of the polypeptide chain.

Reading a Codon Table: 1st base (rows), 2nd base (columns), 3rd base (within cell). Locate the first two bases to find the correct box, then use the third base to identify the specific codon and corresponding amino acid.

Second base in codon

First base in codon	U	C	A	G	Last base in codon
U	UUU Phe	UCU Ser	UAU Tyr	UGU Cys	U
	UUC Phe	UCC Ser	UAC Tyr	UGC Cys	C
	UUA Leu	UCA Ser	UAA STOP	UGA STOP	A
	UUG Leu	UCG Ser	UAG STOP	UGG Trp	G
C	CUU Leu	CCU Pro	CAU His	CGU Arg	U
	CUC Leu	CCC Pro	CAC His	CGC Arg	C
	CUA Leu	CCA Pro	CAA Gln	CGA Arg	A
	CUG Leu	CCG Pro	CAG Gln	CGG Arg	G
A	AUU Ile	ACU Thr	AAU Asn	AGU Ser	U
	AUC Ile	ACC Thr	AAC Asn	AGC Ser	C
	AUA Ile	ACA Thr	AAA Lys	AGA Arg	A
	AUG Met (start)	ACG Thr	AAG Lys	AGG Arg	G
G	GUU Val	GCU Ala	GAU Asp	GGU Gly	U
	GUC Val	GCC Ala	GAC Asp	GGC Gly	C
	GUA Val	GCA Ala	GAA Glu	GGA Gly	A
	GUG Val	GCG Ala	GAG Glu	GGG Gly	G

Figure 4. The mRNA codon table: each triplet codon specifies one amino acid.

Practice: Deducing an Amino Acid Sequence

The following mRNA sequence codes for a short polypeptide: **5' - AUG - UUU - GGC - UAA - 3'** Using a codon table, deduce the sequence of amino acids produced. **Answer:**

Met - Phe - Gly - (stop)

D1.2 Protein Synthesis (HL)

Mutations that Change Protein Structure

Gene mutation: A change to the base sequence of a gene. A point mutation alters a codon and may change the amino acid inserted during translation.

Example: Sickle Cell Disease Sickle cell disease is caused by a point mutation, a classic example of how one base change can alter protein function.

- Single base substitution in the β-globin gene: DNA codon GAG → GTG
- mRNA codon changes: GAG → GUG
- 6th amino acid: glutamic acid → **valine**
- Valine is hydrophobic: haemoglobin molecules clump in low-O_2 conditions
- Red blood cells distort into sickle shape → block capillaries → anaemia

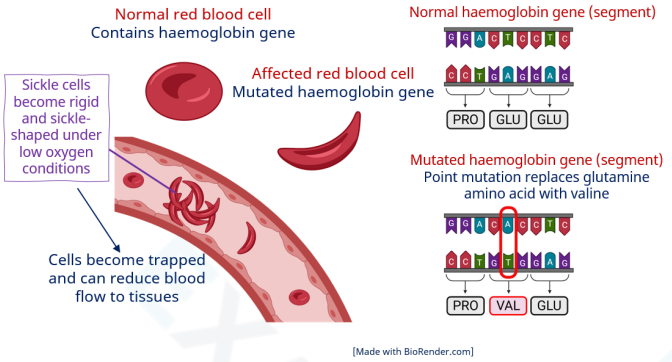


Figure 5. The sickle cell point mutation: one base change alters one amino acid, distorting red blood cell shape.

Directionality of Transcription and Translation

DNA and RNA strands have directionality due to the asymmetry of the sugar-phosphate backbone - one end has a free 5′ phosphate, the other a free 3′ hydroxyl group.

- **Transcription:** RNA polymerase reads the template strand **3′→5′**, synthesising mRNA in the **5′→3′** direction
- **Translation:** Ribosomes move along mRNA in the **5′→3′** direction; new amino acids are always added to the 3′ end of the growing polypeptide
- New nucleotides are always added to the **3′ end** of the growing strand

Initiation of Transcription at the Promoter

- **Promoter:** Non-coding DNA sequence upstream (5′) of a gene; binding site for RNA polymerase
- **Transcription factors** bind to the promoter and recruit RNA polymerase - students are not required to name specific transcription factors
- **Activator sequences** within the promoter encourage RNA polymerase binding → transcription occurs
- **Repressor sequences** prevent RNA polymerase binding → transcription is blocked
- Different cells express different genes by controlling which transcription factors are produced

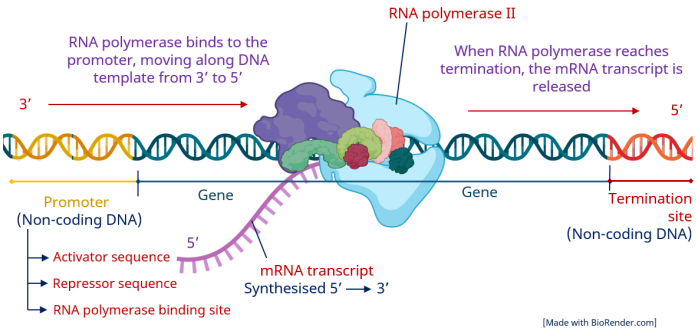


Figure 6. Initiation of transcription: transcription factors bind the promoter and recruit RNA polymerase II. RNA polymerase reads the DNA template strand (3′ to 5′) and synthesizes mRNA (5′ to 3′) until a termination sequence is reached.

Non-Coding Sequences in DNA

Not all DNA codes for polypeptides. Non-coding sequences include:

- **Introns:** Intervening sequences within genes; removed during post-transcriptional modification
- **Telomeres:** Repetitive sequences at chromosome ends; protect coding sequences from being lost during replication
- **Genes for tRNA and rRNA:** Transcribed but not translated
- **Regulatory sequences:** Enhancers and silencers that control gene expression (e.g. promoters)

Post-Transcriptional Modification in Eukaryotes

In eukaryotes, the initial RNA transcript (pre-mRNA) must be modified before leaving the nucleus as mature mRNA. **Three modifications:**

1. **5′ cap:** Modified guanine nucleotide added to 5′ end; protects mRNA from degradation and assists ribosome binding
2. **PolyA tail:** 100–200 adenine nucleotides added to 3′ end; stabilises mRNA and prevents degradation
3. **RNA splicing:** Introns removed and exons spliced together by the **spliceosome**; produces a continuous coding sequence for translation

Alternative Splicing: Different combinations of exons can be joined from the same pre-mRNA, allowing **one gene to produce multiple polypeptides**. This increases proteome diversity without increasing genome size.

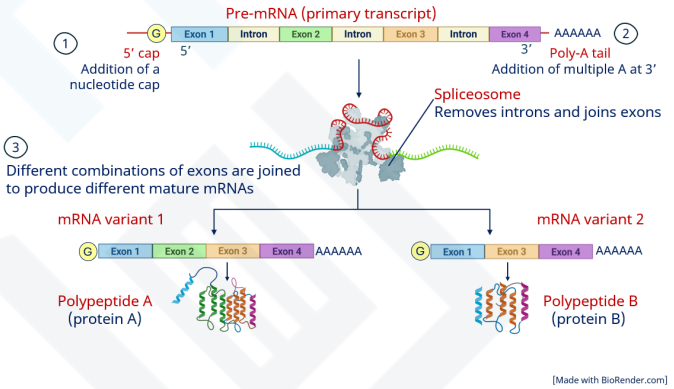


Figure 7. Post-transcriptional modification of pre-mRNA in eukaryotes, including 5′ capping, polyadenylation, RNA splicing, and alternative splicing to produce different polypeptides.

Initiation of Translation

1. Initiator tRNA carrying methionine associates with the small ribosomal subunit
2. The complex binds the **5′ cap** and scans along the mRNA in the 5′→3′ direction
3. Scanning stops at the **AUG start codon**; the initiator tRNA base-pairs with AUG
4. The **large ribosomal subunit** joins, forming the complete ribosome with A, P, and E sites
5. Elongation proceeds as tRNAs move A→P→E; empty tRNAs exit via the E site, and the ribosome translocates along the mRNA until a stop codon is reached

Three tRNA binding sites on the large subunit:

- **A site (aminoacyl):** Incoming tRNA with amino acid binds here
- **P site (peptidyl):** tRNA holding growing polypeptide chain
- **E site (exit):** Empty tRNA exits the ribosome here

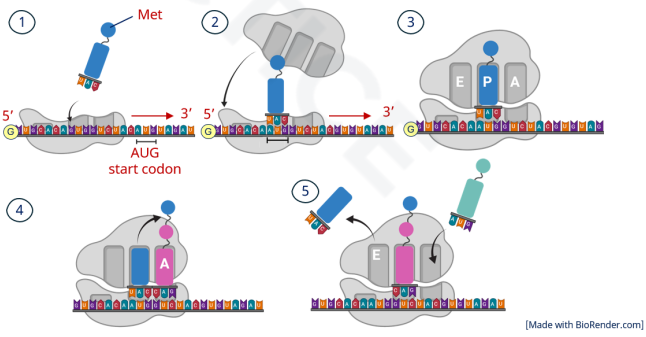


Figure 8. Initiation of translation: small subunit scans mRNA to AUG; large subunit joins forming the complete ribosome with A, P and E sites.

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D1.2 Protein Synthesis (HL)

Modification of Polypeptides into their Functional State

Many polypeptides must be modified after translation before they can function. The two-stage modification of pre-proinsulin to insulin is a key example:

1. **Stage 1: Signal peptide removal:** Pre-proinsulin is synthesised at the ribosome; the signal peptide is removed, producing **proinsulin**
2. **Stage 2: C-peptide cleavage:** The C-peptide is cleaved by proteases, leaving the A and B chains linked by disulfide bonds

Mature insulin consists of the A chain and B chain linked by disulfide bonds and is now functional.

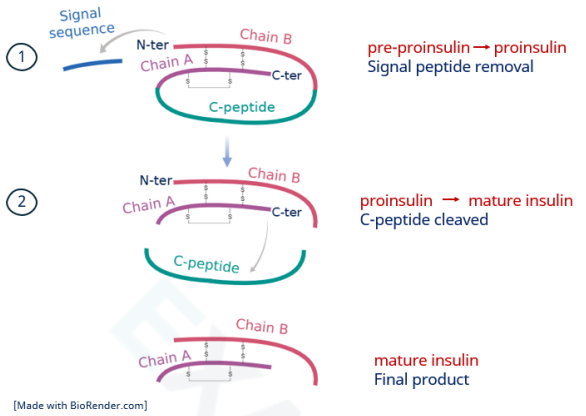


Figure 9. Conversion of pre-proinsulin to mature insulin by removal of the signal peptide and C-peptide.

Recycling of Amino Acids by Proteasomes

- **Proteome:** Complete set of proteins expressed by a cell; must be constantly maintained
- Sustaining a functional proteome requires **constant protein breakdown and synthesis**

How it works:

- Damaged, misfolded, or unneeded proteins are tagged (with ubiquitin)
- **Proteasomes:** Barrel-shaped complexes that recognise tagged proteins
- Tagged proteins are broken down into short peptides
- Peptides further digested, releasing amino acids for **reuse** in new protein synthesis

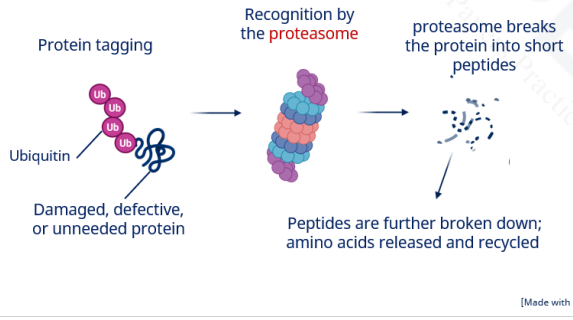


Figure 10. Proteins tagged with ubiquitin are degraded by the proteasome and recycled into amino acids.

Key Terminology

These are the key terms you need to know for **D1.2 Protein Synthesis (HL):**

Transcription	Translation	RNA polymerase
Template strand	mRNA	tRNA
rRNA	Ribosome	Codon
Anticodon	Peptide bond	Polypeptide
Start codon	Stop codon	Degeneracy
Universality	Triplet code	Gene expression
Point mutation	Sickle cell disease	Gene
Promoter	Transcription factor	Intron
Exon	Spliceosome	5′ cap
PolyA tail	Alternative splicing	A site
P site	E site	Proteasome
Proteome	Telomere	Pre-mRNA
Directionality	Pre-proinsulin	Signal peptide

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