From DNA to Protein: Gene Expression
Identification of a gene product as a protein began with a mutation.

Archibald Garrod saw a disease phenotype—alkaptonuria—occurring in children who shared more alleles as first cousins.

A substance in their blood accumulated—was not catalyzed—and the gene for the enzyme was mutated.

Garrod correlated one gene to one enzyme.
Phenylketonuria is another genetic disease that involves this pathway.

The enzyme that converts phenylalanine to tyrosine is nonfunctional.

Untreated, it can lead to mental retardation, but is easily detected in newborns.
Concept 10.1 Genetics Shows That Genes Code for Proteins

Phenotypic expression of alkapatanuria and phenylketonuria led to the *one gene–one protein* hypothesis.

*A mutant phenotype arises from a change in the protein’s amino acid sequence.*

However, the one gene–one protein hypothesis proved too simple in studies of human mutations.
The gene–enzyme relationship has since been revised to the **one gene–one polypeptide relationship**.

Example: In hemoglobin, each polypeptide chain is specified by a separate gene.

Other genes code for RNA but are not translated to polypeptides; some genes are involved in controlling other genes.
Hemoglobin and Sickle Cell Anemia

Hemoglobin Stats:
- quaternary structure of 2 α and 2 β chains
- β chain = 146 amino acids (? Nucleotides)

Sickle Cell Anemia:
- point mutation in a β chain
- autosomal recessive
- heterozygote advantage (malaria resistance)
Figure 10.2 Gene Mutations and Amino Acid Changes

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Variants of β-globin
Molecular biology is the study of nucleic acids and proteins. It often focuses on gene expression.

Gene expression to form a specific polypeptide occurs in two steps:

- **Transcription**—copies information from a DNA sequence (a gene) to a complementary RNA sequence

- **Translation**—converts RNA sequence to amino acid sequence of a polypeptide
Roles of three kinds of RNA in protein synthesis:

- **Messenger RNA (mRNA)** and transcription—carries copy of a DNA sequence to the site of protein synthesis at the ribosome

- **Ribosomal RNA (rRNA)** and translation—catalyzes peptide bonds between amino acids

- **Transfer RNA (tRNA)** mediates between mRNA and protein—carries amino acids for polypeptide assembly
Figure 10.3 From Gene to Protein
Transcription—the formation of a specific RNA sequence from a specific DNA sequence—requires some components:

- A DNA *template* for base pairings—one of the two strands of DNA
- *Nucleoside triphosphates* (ATP,GTP,CTP,UTP) as substrates
- An RNA *polymerase* enzyme
Besides mRNAs, other types of RNA are produced by transcription:

- tRNA
- rRNA
- Small nuclear RNAs
- microRNAs

RNAs may have other functions in the cell besides protein synthesis.
RNA polymerases catalyze synthesis of RNA from the DNA template.

RNA polymerases are *processive*—a single enzyme-template binding results in polymerization of hundreds of RNA bases.

Unlike DNA polymerases, RNA polymerases *do not need primers.*
Transcription occurs in three phases:

- Initiation
- Elongation
- Termination
Initiation requires a promoter—a special sequence of DNA.

RNA polymerase binds to the promoter.

Promoter tells RNA polymerase two things:

- Where to start transcription
- Which strand of DNA to transcribe

Part of each promoter is the transcription initiation site.
Figure 10.5 DNA Is Transcribed to Form RNA (Part 1)
Figure 10.5  DNA Is Transcribed to Form RNA (Part 2)
Elongation: RNA polymerase unwinds DNA about 13 base pairs at a time; reads template in 3′-to-5′ direction.

RNA polymerase adds nucleotides to the 3′ end of the new strand.

The first nucleotide in the new RNA forms its 5′ end and the RNA transcript is antiparallel to the DNA template strand.

RNA polymerases can proofread, but allow more mistakes.
Figure 10.5 DNA Is Transcribed to Form RNA (Part 3)

(B) ELONGATION

5’
3’

Exiting DNA

5’

Exiting RNA transcript

Direction of transcription

3’

Ribonucleoside triphosphates (ATP, UTP, CTP, GTP)

PRINCIPLES OF LIFE, Figure 10.5 (Part 3)
**Termination** is specified by a specific DNA base sequence.

Mechanisms of termination are complex and varied.

For some genes, the transcript falls away from the DNA template and RNA polymerase—for others a helper protein pulls it away.
Figure 10.5  DNA Is Transcribed to Form RNA (Part 4)
**Concept 10.2 DNA Expression Begins with Its Transcription to RNA**

*Coding regions* are sequences of a DNA molecule that are expressed as proteins.

Eukaryotic genes may have noncoding sequences—*introns* (*intervening regions*).

The coding sequences are *exons* (*expressed regions*).

Introns and exons appear in the primary mRNA transcript—*pre-mRNA*; introns are removed from the final mRNA.
Figure 10.6 Transcription of a Eukaryotic Gene (Part 1)
Nucleic acid hybridization reveals introns.

Target DNA is denatured, then incubated with a probe—a nucleic acid strand from another source.

If the probe has a complementary sequence, a probe–target double helix—called a hybrid—forms.
Figure 10.7 Nucleic Acid Hybridization
Researchers using mature mRNA as the probe saw loops where base pairing did not occur in the DNA–RNA hybrid.

If pre-mRNA was used, the result was a linear matchup—complete hybridization.

Introns were a part of the pre-mRNA, but were removed before primary mRNA was made.
Figure 10.8 Demonstrating the Existence of Introns

**INVESTIGATION**

**HYPOTHESIS**

All regions within the coding sequence of a gene end up in its mRNA.

**METHOD**

Gene without intron:
- Double-stranded DNA
- Exon 1
- Exon 2

Gene with intron:
- Exon 1
- Intron
- Exon 2

β-globin mRNA from mature mRNA transcript of exons 1 and 2

**RESULTS**

- Exon 1
- mRNA
- Exon 2

Non-template strand

Electron micrograph of mRNA-DNA hybrid

**CONCLUSION**

The DNA contains noncoding regions within the genes that are not present in the mature mRNA.
Introns *interrupt*, but do not *scramble*, the DNA sequence that encodes a polypeptide.

Sometimes, the separated exons code for different **domains** (functional regions) of the protein.
RNA splicing removes introns and splices exons together.

Newly transcribed pre-mRNA is bound at ends by snRNPs—small nuclear ribonucleoprotein particles.

Consensus sequences are short sequences between exons and introns, bound by snRNPs.
Besides the snRNPs, other proteins are added to form an RNA–protein complex, the spliceosome.

The complex cuts pre-mRNA, releases introns, and splices exons together to produce mature mRNA.
Figure 10.9 The Spliceosome: An RNA Splicing Machine
In the disease $\beta$-thalassemia, a mutation may occur at an intron consensus sequence in the $\beta$-globin gene—the pre-mRNA cannot be spliced correctly.

Non-functional $\beta$-globin mRNA is produced, which shows how mutations are used to elucidate cause-and-effect relationships.

Alternative splicing results in different mRNAs and different polypeptides from a single gene.
While the pre-mRNA is in the nucleus it undergoes two processing steps:

A 5′ cap (or G cap) is added to the 5′ end as it is transcribed and facilitates binding and prevents breakdown by enzymes.

A poly A tail is added to the 3′ end at the end of transcription and assists in export from the nucleus and aids stability.
The **genetic code**—specifies which amino acids will be used to build a protein

**Codon**—a sequence of three bases; each codon specifies a particular amino acid

**Start codon**—AUG—initiation signal for translation

**Stop codons**—UAA, UAG, UGA—stop translation and polypeptide is released
**INVESTIGATION**

**HYPOTHESIS**
A triplet codon based on three-base codons specifies amino acids.

**METHOD**

![Diagram showing codons and their corresponding amino acids](Image)

**RESULTS**

- `UUUUUUUUUUU` specifies Phe, Phe, Phe
- `AAAAAAAAAAA` specifies Lys, Lys, Lys
- `CCCCCCCCCCC` specifies Pro, Pro, Pro

**CONCLUSION**

- `UUU` is an mRNA codon for phenylalanine.
- `AAA` is an mRNA codon for lysine.
- `CCC` is an mRNA codon for proline.
### Figure 10.11 The Genetic Code

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<th>Second letter</th>
<th>Third letter</th>
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**PRINCIPLES OF LIFE, Figure 10.11**

For most amino acids, there is more than one codon; the genetic code is *redundant*.

The genetic code is not *ambiguous*—each codon specifies only one amino acid.

The genetic code is nearly universal: the codons that specify amino acids are the same in all organisms.

Exceptions: Within mitochondria, chloroplasts, and some protists, there are differences.
This common genetic code is a common language for evolution.

The code is ancient and has remained intact throughout evolution.

The common code also facilitates genetic engineering.
Mutations can also be defined in terms of their effects on polypeptide sequences.

*Silent mutations* have no effect on amino acids—often found in noncoding regions of DNA.

A base substitution does not always affect amino acid sequence, which may be repaired in translation.
Figure 10.12 Mutations (Part 1)

**Silent mutation**

Mutation at position 12 in DNA: A instead of C

DNA template strand

```
3' TACACCAGGGAATACTAATT
5'
```

Transcription

mRNA

```
5' AUGUGGCUCCUCUGAUA
3'
```

Translation

Polypeptide

```
Met Trp Leu Pro Asp Stop
```

*Result:* No change in amino acid sequence
Missense mutations are substitutions by one amino acid for another in a protein.

Example: Sickle-cell disease—allele differs from normal by one base pair

Missense mutations may result in a defective protein, reduced protein efficiency, or even a gain of function as in the TP53 gene.
Figure 10.12 Mutations (Part 2)

**Missense mutation**

Mutation at position 14 in DNA: A instead of T

DNA template strand

3’ TACACCGGAGGGGCCC AATT 5’

Transcription

mRNA

5’ AUGUGGGCUCCCGGGUUAAA 3’

Translation

Polypeptide

Met Trp Leu Pro Val Stop

Result: Amino acid change at position 5; Val instead of Asp
Nonsense mutations involve a base substitution that causes a stop codon to form somewhere in the mRNA.

This results in a shortened protein, which is usually not functional—if near the 3' end it may have no effect.
Figure 10.12  Mutations (Part 3)

**Nonsense mutation**

Mutation at position 5 in DNA: T instead of C

DNA template strand

\[ \begin{align*}
T & \quad A & \quad C & \quad A & \quad T & \quad C & \quad G & \quad A & \quad G & \quad G & \quad G & \quad C & \quad C & \quad T & \quad A & \quad A & \quad T \\
3' & & & & & & & & & & & & & & & & 5'
\end{align*} \]

Transcription

mRNA

\[ \begin{align*}
A & \quad U & \quad G & \quad U & \quad A & \quad G & \quad C & \quad U & \quad C & \quad C & \quad C & \quad G & \quad G & \quad A & \quad U & \quad U & \quad A \\
5' & & & & & & & & & & & & & & & & 3'
\end{align*} \]

Translation

Polypeptide

Result: Only one amino acid translated; no protein made

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*PRINCIPLES OF LIFE, Figure 10.12 (Part 3)*

Frame-shift mutations are insertions or deletions of bases in DNA.

These mutations interfere with translation and shift the “reading-frame.”

Nonfunctional proteins are produced.
Figure 10.12 Mutations (Part 4)

Frame-shift mutation

Mutation by insertion of T between bases 6 and 7 in DNA

Normal DNA template strand

```
3' TACACCGAGGGGCCCTAATT 5'
```

Mutant DNA template strand

```
3' TACACCTGAGGGGCCCTAATT 5'
```

Transcription

```
mRNA 5' AUGUGGACUCCCCGGAUUAA 3'
```

Translation

```
Polypeptide

Met Trp Thr Pro Gly Leu
```

Result: All amino acids changed beyond the point of insertion
tRNA links information in mRNA codons with specific amino acids.

For each amino acid, there is a specific type or “species” of tRNA.

Two key events to ensure that the protein made is the one specified by the mRNA:

• tRNAs must read mRNA codons correctly.

• tRNAs must deliver amino acids corresponding to each codon.
Each tRNA has three functions, made possible by its structure and base sequence:

- tRNAs bind to a particular amino acid, and become “charged.”
- tRNAs bind at their midpoint—anticodon-to mRNA molecules.
- tRNAs interacts with ribosomes.
Concept 10.4 Translation of the Genetic Code Is Mediated by tRNA and Ribosomes

*Wobble*—specificity for the base at the 3′ end of the codon is not always observed.

Example: Codons for alanine—GCA, GCC, and GCU—are recognized by the same tRNA.

Wobble allows cells to produce fewer tRNA species, but does not allow the genetic code to be ambiguous.
Activating enzymes—*aminoacyl-tRNA synthetases*—charge tRNA with the correct amino acids.

Each enzyme is highly specific for one amino acid and its corresponding tRNA.

The enzymes have three-part active sites—they bind a specific amino acid, a specific tRNA, and ATP.
Experiment by Benzer and others:

Cysteine already bound to tRNA was chemically changed to alanine.

Which would be recognized—the amino acid or the tRNA in protein synthesis?

Answer: Protein synthesis machinery recognizes the anticodon, not the amino acid
The translation of mRNA by tRNA is accomplished at the **ribosome**—the workbench—and holds mRNA and charged tRNAs in the correct positions to allow assembly of polypeptide chain.

Ribosomes are not specific; they can make any type of protein.
Ribosomes have two subunits, large and small.

In eukaryotes, the large subunit has three molecules of ribosomal RNA (rRNA) and 49 different proteins in a precise pattern.

The small subunit has one rRNA and 33 proteins.
Figure 10.14 Ribosome Structure
Large subunit has three tRNA binding sites:

A (amino acid) site binds with anticodon of charged tRNA.

P (polypeptide) site is where tRNA adds its amino acid to the growing chain.

E (exit) site is where tRNA sits before being released from the ribosome.
Ribosome has a *fidelity function*: when proper binding occurs, hydrogen bonds form between the base pairs.

Small subunit rRNA validates the match—if hydrogen bonds have not formed between all three base pairs, the tRNA must be an incorrect match for that codon and the tRNA is rejected.
Like transcription, translation also occurs in three steps:

- **Initiation**
- **Elongation**
- **Termination**
Initiation:

An **initiation complex** consists of a charged tRNA and small ribosomal subunit, both bound to mRNA.

After binding, the small subunit moves along the mRNA until it reaches the start codon, AUG.

The first amino acid is always methionine, which may be removed after translation.
The large subunit joins the complex; the charged tRNA is now in the P site of the large subunit.

*Initiation factors* are responsible for assembly of the initiation complex from mRNA, two ribosomal subunits and charged tRNA.
Figure 10.15 The Initiation of Translation (Part 1)
**Elongation**: The second charged tRNA enters the A site.

Large subunit catalyzes two reactions:

It breaks bond between tRNA in P site and its amino acid.

A peptide bond forms between that amino acid and the amino acid on tRNA in the A site.
When the first tRNA has released its methionine, it moves to the E site and dissociates from the ribosome—it can then become charged again.

Elongation occurs as the steps are repeated, assisted by proteins called *elongation factors*. 
The large subunit has **peptidyl transferase** activity—if rRNA is destroyed, the activity stops.

The component with this activity is an rRNA in the ribosome.

The catalyst is an example of a *ribozyme* (from *ribonucleic acid* and *enzyme*).
Figure 10.16 The Elongation of Translation (Part 2)
**Termination**—translation ends when a stop codon enters the A site.

Stop codon binds a *protein release factor*—allows hydrolysis of bond between polypeptide chain and tRNA on the P site.

Polypeptide chain separates from the ribosome—C terminus is the last amino acid added.
Figure 10.17 The Termination of Translation (Part 1)
### Table 10.2 Signals that Start and Stop Transcription and Translation

<table>
<thead>
<tr>
<th></th>
<th>Transcription</th>
<th>Translation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiation</td>
<td>Promoter DNA</td>
<td>AUG start codon in the mRNA</td>
</tr>
<tr>
<td>Termination</td>
<td>Terminator DNA</td>
<td>UAA, UAG, or UGA in the mRNA</td>
</tr>
</tbody>
</table>
Several ribosomes can work together to translate the same mRNA, producing multiple copies of the polypeptide.

A strand of mRNA with associated ribosomes is called a **polyribosome**, or **polysome**.
Posttranslational aspects of protein synthesis:

Polypeptide emerges from the ribosome and folds into its 3-D shape.

Its conformation allows it to interact with other molecules—it may contain a **signal sequence** (or *signal peptide*) indicating where in the cell it belongs.
In the absence of a **signal sequence**, the protein will remain where it was made.

Some proteins contain signal sequences that “target” them to the nucleus, mitochondria, or other places.

Signal sequence binds to a receptor protein on the organelle surface—a channel forms and the protein moves into the organelle.
Figure 10.19 Destinations for Newly Translated Polypeptides in a Eukaryotic Cell (Part 1)
Figure 10.20  Testing the Signal

INVESTIGATION

HYPOTHESIS
A nuclear localization signal (NLS) is necessary for import of a protein into the nucleus.

METHOD
1. A protein labeled with a fluorescent dye is injected into the cytoplasm.

RESULTS
Injected protein:
- Nucleoplasm, a nuclear protein, with the NLS
- Nucleoplasm with the NLS removed
- Pyruvate kinase, a cytoplasmic protein without the NLS
- Pyruvate kinase, attached NLS

CONCLUSION
The NLS is essential for nuclear protein import and will direct a normally cytoplasmic protein to the nucleus.

PRINCIPLES OF LIFE, Figure 10.20
Protein modifications:

**Proteolysis**—cutting of a long polypeptide chain, or *polyprotein*, into final products, by *proteases*

**Glycosylation**—addition of carbohydrates to form glycoproteins

**Phosphorylation**—addition of phosphate groups catalyzed by *protein kinases*—charged phosphate groups change the conformation of the protein
Figure 10.21 Posttranslational Modifications of Proteins

The diagram illustrates the process of posttranslational modifications of proteins, which include:

- **Translation**
- **Posttranslational processing**
- **Proteolysis**
- **Glycosylation**
- **Phosphorylation**
Tetracyclines kill bacteria by interrupting translation.

They bind to the small subunit of the ribosome, which changes the ribosome structure.

 Charged tRNAs can no longer bind to the A site on the ribosome.
Figure 10.22 An Antibiotic at the Ribosome