PROTEIN EVOLVED!
Beadle and Tatum

One Gene One Enzyme Hypothesis.

Examination of bread mold with mutations induced by radiation
Gene – region of DNA that controls the synthesis of a particular product, whether it’s an enzyme, hormone, or structure of a cell.

Phenotype – the physical characteristic exhibited by an organism.

All of the products listed above are types of Proteins.
What are Proteins?

Proteins are molecules made of long chains of Amino Acids.

The amino acids are held together by special types of bonds called **Peptide bonds**, many amino acids held together by many peptide bonds are called **Polypeptides**.
One Gene

One Polypeptide Hypothesis

Each gene carries the information for one particular polypeptide chain.

There are roughly 20-30,000 genes on the 23 pairs of human chromosomes.
Amino Acids

There are 20 amino acids that make up polypeptides.

These amino acids are like letters within a protein alphabet – we have 26 letters in our alphabet that make up words.
Codon

The three bases that code for a particular amino acid.
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Protein Synthesis

Two step dance…transcription the making of RNA from DNA (photocopy of instructions)

Translation – the organelles reading the instructions to make protein.
RNA

Ribonucleic Acid – an intermediary molecule that takes the blueprints from DNA in the nucleus and brings the information to the Ribosomes in the cell.

RNA is similar to DNA with three major differences:

- The sugar that makes up RNA is Ribose instead of Deoxyribose
- There is a different base called Uracil. Uracil replaces Thymine.
- RNA is usually single stranded.
Three Types of RNA

mRNA – Messenger RNA. A short region of RNA that copies the DNA blueprint.

tRNA – Transfer RNA. Each t RNA is associated with a single amino acid.

rRNA – Ribosomal RNA. RNA that combines with proteins to make a complete Ribosome.
mRNA
tRNA

Site of amino acid attachment

Hydrogen bonds

Anticodon
Protein Synthesis

Step 1

**Transcription** is the process in which **RNA polymerase** synthesizes RNA by using one strand of a DNA molecule as a template.
RNA Polymerase

- RNA Pol I makes rRNA
- RNA Pol II makes mRNA
- RNA Pol III makes tRNA
DNA is unwound at a promoter site by the enzyme RNA polymerase.

**Promoter Site** - Area on the DNA that indicates where transcription is going to start. The STARTING POINT

**Start Codon** - TAC
The portion of the DNA that is transcribed into an RNA molecule is called a **transcription unit**.

An enzyme called **RNA polymerase** carries out transcription. With the help of **protein transcription factors**, it attaches to the beginning of a region of the DNA called the **promoter**, pries the DNA strands apart, and untwists a short portion of the double helix.
RNA polymerase moves along the DNA, pairing up RNA nucleotides with their DNA complements-- adding nucleotides to the end of the growing RNA molecule.
Here's a close-up view of **elongation**.

Only one DNA strand-- the template strand-- serves as a template for RNA synthesis.

**RNA polymerase** moves along the DNA strand in the 3' to 5' direction, adding nucleotides to the 3' end of the RNA chain. Note that U in RNA pairs with A in DNA.
Elongation: mRNA is made from DNA in a transcription bubble. Bases are added by RNA pol using the same base pairing rules as DNA.

Termination: stop signal - stops RNA polymerase

The RNA Polymerase will continue to make mRNA until it hits the termination signal.

At the termination signal the mRNA is complementary to itself, it wraps around itself forming a kink... the polymerase then falls off the DNA.
Once RNA polymerase has gone past a sequence called the terminator at the end of the transcription unit, the enzyme releases the completed RNA and detaches from the DNA.
RNA Processing

In eukaryotic cells, the RNA transcript is modified before translation. This step is called RNA processing.

mRNA is changed before it leaves the nucleus and heads toward the Ribosomes.
**RNA processing** begins with alteration of the ends of the RNA.

A 5' **Methyl cap** consisting of a modified guanine nucleotide is added to the 5' end.

A **poly-A tail** made of 30 to 200 adenine nucleotides is added to the 3' end.
RNA processing continues with the removal of portions of the coding segment that do not actually code for protein. This process is carried out by small nuclear ribonucleoproteins--snRNPs, or "snurps"-- which join with other proteins to form large structures called spliceosomes.
The snRNPs join with other proteins to form **spliceosomes**. (For simplicity, only one spliceosome is shown here.)
Spliceosomes delete portions of the RNA called introns, and connect the remaining segments, which are called exons, to form a finished messenger RNA molecule.

The mRNA leaves the nucleus and enters the cytoplasm, where translation of the RNA message into protein occurs.
RNA transcript (pre-mRNA)

Exon 1

Intron

Exon 2

Other proteins

snRNA

snRNPs

Spliceosome

Spliceosome components

mRNA

5’

Exon 1

Exon 2

Cut-out intron

1. Protein

2. snRNA

3. Other proteins

4. SnRNPs

5. Spliceosome

6. Spliceosome components

7. mRNA

8. 5’
Much of DNA is non-coding base sequences, not genes

**Intron:** part of gene (DNA or mRNA) that does not code for polypeptide.

It must be removed before translation.

**Exon:** coding part of DNA (or mRNA). This is the gene!

The exon is translated during protein synthesis.

(Klug & Cummings 1997)
mRNA Modification

mRNA is transcribed from DNA in the nucleus.

In Eukaryotes it is modified before it is sent to the Ribosome.

1\textsuperscript{st} a Methyl Group is put on the front –indicates where the Ribosome should start Protein Synthesis.

2\textsuperscript{nd} the Introns are excised or removed.

3\textsuperscript{rd} a tail of Adenines is placed onto the mRNA
mRNA Anatomy

- A modified guanine nucleotide added to the 5’ end
- 50 to 250 adenine nucleotides added to the 3’ end
- Protein-coding segment
- Polyadenylation signal
- 5’ Cap
- 5’ UTR
- Start codon
- Stop codon
- 3’ UTR
- 3’
- Poly-A tail

TRANSCRIPTION
DNA
Pre-mRNA
mRNA
RNA PROCESSING
mRNA
Ribosome
TRANSLATION
Polypeptide
mRNA Anatomy
Ribosome
Polypeptide
Translation

Translation, is the process of assembling proteins from information encoded in mRNA.

In translation, a cell reads an mRNA message and assembles a polypeptide accordingly.

Translation occurs at the Ribosomes in the cell's cytoplasm.
Here's how translation occurs.

As an mRNA strand slides though a ribosome, triplets of RNA bases spell out the amino acid sequence of a polypeptide. It is the job of transfer RNA molecules to match RNA bases with the correct amino acids.
Ribosomes actually come in two parts, a large and small subunit.

The mRNA from the nucleus comes along and binds to the small subunit.
After the mRNA binds to the small subunit the large subunit comes together making a complete Ribosome.
There are two sites inside the Ribosome:

The P Site and the A Site
The P site or Peptidal Site is just large enough to expose a 3 Base codon.

The three base codon indicates what amino acid should be placed in the protein.
A tRNA with the complementary base sequence to the exposed mRNA can fit into this p site.

The tRNA carries with it an amino acid. The Amino Acid is the start of the polypeptide or protein chain.
Another tRNA with the complementary sequence to the exposed mRNA is the A or Acyl site will come along next.

The second tRNA is also carrying an amino acid. This will be bonded to the first amino acid by a peptide bond.
tRNA is a looped molecule that holds a specific amino acid at the top and has a complementary “anticodon” at the bottom.

The anti codon corresponds to the codons on the mRNA.
• A specific enzyme called an aminoacyl-tRNA synthetase
  – Joins each amino acid to the correct tRNA
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Elongation of the polypeptide now occurs, with amino acids being added one by one. The **codon** in the A site of the ribosome pairs with the **anticodon** of the appropriate **tRNA molecule**.
Part of the ribosome catalyzes the formation of a peptide bond between the amino acid extending from the P site and the amino acid extending from the A site.
The tRNA in the A site now translocates to the P site. The tRNA that was in the P site moves to the E site and exits from the ribosome. Meanwhile, a new tRNA brings its amino acid to the A site and the process is repeated.
The new polypeptide or protein forms out of the “P” site.
Stop Codons

Three Codons that do not code for anything. No tRNA binds with them.

When the Ribosome reaches them, the Ribosome falls off, Translation stops.

Stop Codons: UAA UAG UGA
Three special base triplets—UAA, UAG, and UGA—do not code for amino acids, but instead act as stop codons, which terminate the process of translation. A protein called a release factor binds to the stop codon in the A site. It acts to free the completed polypeptide from the tRNA that is in the P site, and the translation assembly comes apart.
Ribosomes add 15 amino acids per second.

There is an error rate of 1 error for every 9000 amino acids.

What is a mistake in Protein Synthesis called?

A Mutation.
Polyribosomes

- A number of ribosomes can translate a single mRNA molecule simultaneously
  - Forming a polyribosome

(a) An mRNA molecule is generally translated simultaneously by several ribosomes in clusters called polyribosomes.

(b) This micrograph shows a large polyribosome in a prokaryotic cell (TEM).
Structure of Hair

• Keratin
  – Fibrous structural protein
Mutation

A mutation is any change in the nucleotide-base sequence of a gene or DNA molecule.

Silent Mutation - a change in the DNA sequence that cannot be seen.
Silent Mutation

Wobble position, the third base within a codon often does not matter in which amino acid the codon codes for.

For example; a change from GCA to GCC still yields the amino acid alanine.
Missense Mutation

A mutation that causes the substitution of two similarly shaped amino acids (with similar chemical properties) within a polypeptide, this would have little or no effect on protein structure/function.
Non Sense Mutation

A mutation that changes a codon from coding for an amino acid to one in which it is a stop codon.

Depending where within the polypeptide, this mutation could cause little or drastic effect.
Types of Mutations

**Frameshift Mutation** - single addition or deletion of a base in the mRNA that moves the reading frame of the Ribosome.

**Point Mutation** - substitution of a base within the genetic code.

****Most Harmful mutations are Frame shift mutations.
Other Mutations

• Mutations outside of coding sequences can also cause problems; they might affect the correct splicing of exons etc.

• If a mutation occurs in a gene encoding for gene expression machinery (Polymerases, Splicesosomes etc.) this is lethal
• A summary of transcription and translation in a eukaryotic cell
Every cell in the body has the same DNA

So how can we account for the massive differences in cells?

The different cell types in a multicellular organism differ dramatically in both structure and function. If we compare a mammalian neuron with a lymphocyte, for example, the differences are so extreme that it is difficult to imagine that
Evidence that a differentiated cell contains all the genetic instructions necessary to direct the formation of a complete organism.
Different Cell Types Synthesize Different Sets of Proteins

• Many processes are common to all cells.

• Some proteins are abundant in the specialized cells in which they function and cannot be detected elsewhere.

• At any one time, a typical human cell expresses approximately 10,000 to 20,000 of its approximately 30,000 genes.
A Cell Can Change the Expression of Its Genes in Response to External Signals
Gene Expression Can Be Regulated at Many of the Steps in the Pathway from DNA to RNA to Protein
Anatomy of a Gene

Regulatory Region

Promoter Site

Exon

Intron

3' UTR Untranslated Region

5' UTR Untranslated Region
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 transport
  5. translation
  6. protein processing
  7. protein degradation
DNA methylation

- **Methylation of DNA** blocks transcription factors
  - no transcription
  - genes turned off
- attachment of methyl groups (−CH₃) to cytosine
  - C = cytosine
- nearly permanent inactivation of genes
  - ex. inactivated mammalian X chromosome = Barr body

![Methylation diagram](image)
Control of Gene Expression

A bacterium can adjust to changes in its environment by controlling gene expression.

An operon is a group of functionally-related genes, along with control sequences, that responds to chemical cues by regulating enzyme production. The lac operon of E. coli responds to changes in food supply-- specifically to the availability of the sugar lactose-- by altering the production of proteins involved in the utilization of lactose.
Positive and Negative Gene Control

• Inducible and Repressible gene regulation can be accomplished by both positive and negative control mechanisms

• **Regulator Gene** – gene product regulates the expression of other genes

• *Positive control* - regulator gene product required to *turn on* expression

• *Negative control* - regulator gene product required to *turn off* expression
Transcription initiation occurs by RNA polymerase binding to promoter

- Regulator Gene products (RPs) act by binding to regulator protein binding site (RPBS) adjacent to promoter
  - Binding to RPBS regulates RNA polymerase/promoter binding
    - In positive control, RPs called *activators* – turn on expression
    - In negative control, RPs called *repressors* – turn off expression
Inducible vs. Repressible Systems

• Inducible systems
  – Resting state: Transcription is OFF

• Repressible systems
  – Resting state: Transcription in ON
Lactose Operon

- Lac operon
  - Negatively controlled inducible operon
Lactose Operon

• *lacI* is the regulator gene
  – Protein product encodes a repressor

  – Binds *lac* operator
    • sterically prevents RNA polymerase from transcribing *lacZ, lacY, and lacA* which will make the enzyme to digest lactose.
Lactose Operon

- Induction of *lac* operon
  - Inducer is allolactose, sensor of lactose

- Allolactose binds repressor
  - Releases from Operator
  - Transcription is INDUCED
Lac Operon
Lac Repressor Protein

This protein is made in the presence and absence of Lactose.

The genes that code for this protein are in the 5’ Regulatory region.
Absence of Lactose

In the absence of Lactose, the Lac Repressor protein binds to the promoter site for Lactase inhibiting transcription.

RNA Polymerase can not bind.
Consequences

RNA polymerase

DNA

no RNA

no proteins made
When Lactose is Present

When lactose is present, some lactose will bind to the repressor protein, changing its shape.

When lactose is present, it acts as an inducer of the operon. It enters the cell and binds to the Lac repressor, inducing a conformational change that allows the repressor to fall off the DNA.
The repressor protein can no longer bind to the promoter site.

Without the repressor in its way RNA Polymerase can hop on to the DNA and transcribe the mRNA for Lactase.
Translation

DNA

mRNA

structural proteins made

lactose
Lactose Intolerance

Lactose intolerance is the inability to digest significant amounts of lactose, the major sugar found in milk.

Lactose intolerance is caused by a shortage of the enzyme lactase, which is produced by the cells that line the small intestine. Lactase breaks down milk sugar into two simpler forms of sugar called glucose and galactose, which are then absorbed into the bloodstream.

Many adults have reduced lactase production leading to symptoms similar to lactose intolerance.
Symptoms

Without the breakdown of lactose-the bacteria of your gut get involved…

Common symptoms, which range from mild to severe, include nausea, cramps, bloating, gas, and diarrhea.
The trp Operon - a repressible system

The trp operon of E. coli controls the biosynthesis of tryptophan in the cell from the initial precursor chorismic acid.

Tryptophan is an important amino acid used to build proteins.

When tryptophan becomes low within an e.coli’s diet the cell starts to synthesize the amino acid. If Tryptophan is present there is no need to synthesize tryptophan.
As with all operons, the trp operon consists of the **repressor, promoter, operator** and the **structural genes**.

In this system, though, unlike the lac operon, the gene for the repressor is not adjacent to the promoter, but rather is located in another part of the E. coli genome.

Another difference is that the operator resides entirely **within the promoter**.
Repressible System

The trp operon is a repressible system. The addition of tryptophan (the effector molecule) to the E. coli environment shuts off the system because the repressors binds at the operator.
No Tryptophan present therefore the repressor is inactive.

Can’t bind to DNA therefore the cell makes tryptophan
Transcription of Tryptophan
Synthesis
Excess

When tryptophan is abundant it binds to the repressor activating it.
When the cell uses up all of the available tryptophan the repressor loses its binding ability and no longer binds to the promoter site...therefore RNA pol binds...
RNA interference

- **Small interfering RNAs (siRNA)**
  - short segments of RNA (21-28 bases)
    - bind to 3’ end of 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
    - Regulates genes after the mRNA has been made – appears to regulate about 50% of our genes.
How it works

To shut off genes the cell makes a mRNA sequence that is complementary to the mRNA that the cell wants to shut off. This makes a double stranded region.

If the cell senses that there is double stranded mRNA it induces the production of DICER (RNase III) which chops up the double stranded RNA into short 22 NT size fragments called miRNA.

miRNA act as a guide molecule. It guides RISC (RNA Inducing Silencing Complex) an enzyme that binds to the primary transcript and destroys the mRNA.
Action of siRNA

- siRNA
- double-stranded miRNA + siRNA
- mRNA degraded
- dicer enzyme
- mRNA for translation
- breakdown enzyme (RISC)
- functionally turns gene off

Hot...Hot new topic in biology
Hormones Regulate Development
Lipophilic Molecules
What is a Steroid?

After, Okamura
Figure 4.3. Chemical structures of ecdysone and 20-hydroxyecdysone compared with structure of cholesterol, from which these hormones arise.
Steroid Nuclear Receptor Complex
How Steroids Work

Steroid

Lipid Bilayer

NR

Binding Site

DNA for Gene A
Allosteric Change

Lipid Bilayer

Steroid

NR

Binding Site

DNA for Gene A
Complex Bound to DNA

Lipid Bilayer

Steroid

NR

Binding Site

DNA for Gene A
Transcription

Lipid Bilayer

Steroid

mRNA codes for protein A

DNA
20 Hydroxyecdysone
Endocrine Disrupters

2,3,7,8 Tetrachlor-dibenzo-p-dioxin

Bis Phenol A
How Endocrine Disrupters Mimics Work

Mimic

Lipid Bilayer

NR Binding Site

DNA for Gene A
Mimic Nuclear Receptor Complex

Lipid Bilayer

Mimic

NR

Binding Site

DNA for Gene A
Allosteric Change

Lipid Bilayer

Mimic

NR

Binding Site

DNA for Gene A
Complex Bound to DNA

Lipid Bilayer

Mimic

NR

Binding Site

DNA for Gene A
Transcription

Lipid Bilayer

Mimic

mRNA codes for protein A

NR

Binding Site

DNA