

The Nature of Genes

Early ideas to explain how genes work came from studying human diseases.

Archibald Garrod proposed that patients with the disease *alkapt-onuria* lacked a particular enzyme.

Beadle and Tatum studied *Neurospora crassa*. They looked for fungal cells lacking specific enzymes.

Beadle and Tatum results was that each mutated enzyme disrupted one key enzyme in the metabolic pathway.

Prokaryotic Transcription

Prokaryotic Transcription: Single RNA polymerase

- Initiation of mRNA synthesis does not require a primer

Prokaryotic Transcription requires a Promoter, Start Site, and a termination site.

Transcription occurs in three major stages:

- Initiation
- Elongation
- Termination

Initiation: RNA polymerase binds to the **promoter**

Promoter: Forms a recognition and binding site for the RNA polymerase.

- Found upstream of the start site.
- Not transcribed.
- *Asymmetrical:* indicate site of initiation and direction of termination.

Prokaryotic Transcription (cont)

Elongation: RNA transcript grows in the 5'-to-3' direction as ribonucleotides are added.

- **Transcription bubble:** contains RNA polymerase, DNA template, and growing RNA transcript.
- After the transcription bubble passes, the now-transcribed DNA is rewound as it leaves the bubble.

Termination: Marked by sequence that signals "stop" to polymerase.

- Causes the formation of phosphodiester bonds to cease.
- RNA-DNA hybrid within the transcription bubble dissociates.
- RNA polymerase releases the DNA.
- DNA rewinds.

Hairpin in RNA causes RNA polymerase to pause

U:A base pairs weaken the DNA/RNA bonding.

Prokaryotic **transcription** is coupled to **translation**

- mRNA begins to be translated before transcription is finished.

Frameshift mutations

- Addition or deletion of a single base
- Much more profound consequences
- Alter reading frame downstream
- Triplet repeat expansion mutation

Hunting disease
Repeat unit is expanded in the disease allele relative to the normal

Transcription and Translation

The Central Dogma Information only flows from: DNA-->RNA-->-protein
First described by Francis Crick.

Transcription DNA--> RNA

- DNA-directed synthesis of RNA
- Only template strand of DNA used
- T in DNA replaced by U in RNA.
- mRNA used to direct synthesis of polypeptides.

Translation - Synthesis of polypeptides.

- Takes place at ribosome.
- Requires several kinds of RNA.

RNA All synthesized from DNA template by transcription

- Messenger RNA (mRNA).
- Ribosomal RNA (rRNA).
- Transfer RNA (tRNA).
- Small nuclear RNA (snRNA)
- Signal recognition particle RNA (SRP RNA).
- Micro-RNA (miRNA).

Eukaryotic Transcription

3 different RNA polymerase!!

RNA polymerase I: Transcribes rRNA.

RNA polymerase II: transcribes mRNA and some snRNA.

RNA polymerase III: transcribes tRNA and some other small RNAs

Each RNA polymerase recognizes its own promoter.

Initiation of transcription:
Requires a series of **transcription factors** (helper).

- **Transcription factors:**
*Necessary to get the RNA polymerase II enzyme to a promoter** and to initiate gene expression.

Elongation: RNA transcribed from the DNA template.

Termination not as well defined.

Initiation of transcription

- Transcription factors bind to a promoter region and recruit RNA polymerase.
- Forms the initiation complex.

Protein Targeting

In eukaryotes, translation may occur in the cytoplasm or the rough endoplasmic reticulum (RER).

Signal sequences at the beginning of the polypeptide sequence bind to the **signal recognition (SRP)**.

- The signal sequence and SRP are recognized by RER receptor proteins
- Docking holds ribosome to RER
- Beginning of the protein-trafficking pathway

Mutation: Altered Genes

Point mutations	alter a single base
Base substitution	substitute one base for another
Silent mutation	same amino acid inserted
Missense mutation	changes amino acid inserted - Transitions - Transversions
Nonsense mutations	changed to stop codon

The Genetic Code

Francis Crick and Sydney Brenner determined how the order of nucleotides in DNA encoded amino acid order.

- They introduced single nucleotide insertions or deletions and looked for mutations (**Frameshift mutations**)

A **Codon** is a block of three DNA nucleotides corresponding to an amino acid,

Spaced Codons: Codon sequence in a gene punctuated.

Unspaced Codons: codons adjacent to each other.

- Marshall Nirenberg identified the codons that specify each amino acid.

Stop Codon: 3 codons (UAA, UGA, UAG) used to terminate translation

Start Codon: Codon (AUG) used to signify the start of translation

The Genetic Code (cont)

Code is **degenerate**: Some amino acids are specified by more than one codon.

Code practically universal:

Strongest evidence that all living things share **common ancestry**.

- Advanced in genetic engineering.
- Mitochondria and chloroplast have some differences in "stop" signals.

mRNA modifications

In **eukaryotes** the primary transcript must be modified to become mature mRNA

Addition of a **5' cap** Protects nucleotides from getting lost, from degradation.

- Involved in translation initiation.

Addition of a **3' poly-A tail** Created by poly-A polymerase, protection from degradation

- Puts whole string of A's (AAA) to protect!

Removal of noncoding sequences (**introns**): Pre-mRNA **splicing** done by spliceosome.

- Cut it out to get rid of it!!!

tRNA charging reaction

Each aminoacyl-tRNA synthetase recognizes only 1 amino acid but several tRNAs.

Charged tRNA has an amino acid added using the energy from ATP.

- Can undergo peptide bond formation without additional energy.

Ribosomes do not verify amino acid attached to tRNA.

tRNA charging reaction (cont)

The **ribosome** has multiple tRNA binding sites:

P site: binds the tRNA attached to the growing peptide chain

A site: binds the tRNA carrying the next amino acid.

E site: binds the tRNA that carried the last amino acid, tRNA exits ribosome.

The **ribosome** has **two primary functions**

- Decode the mRNA.
- Form peptide bonds.

Peptidyl transferase:

- Enzymatic component of the ribosome.
- Forms peptide bonds between amino acids.

Chromosomal mutations

Change the structure of a chromosome

Deletions: part of chromosome is lost

Duplication: part of chromosome is copied

Inversion: part of chromosome in reverse order

Translocation: part of chromosome is moved to a new location

Eukaryotic pre-mRNA splicing

Introns non-coding sequences

Exons sequences that will be translated

Small ribonucleoprotein particles (**snRNPs "snurps"**) Looks for introns and exons and recognizes it.

Eukaryotic pre-mRNA splicing (cont)

Spliceosomes responsible for removing introns

snRNPs cluster with other proteins to form **spliceosome**

tRNA and Ribosomes

tRNA molecules carry amino acids to the ribosome for incorporation into a polypeptide.

- **Aminoacyl-tRNA synthetase** add amino acids to the acceptor stem of tRNA.

- **Anticodon** loop contains 3 nucleotides complementary to mRNA codons.

Translation

Process by which the mRNA transcript is read by the ribosomes and used to make a polypeptide.

Occurs in 3 main stages:

- Initiation
- Elongation
- Termination

There are some important differences between translation in prokaryotes and eukaryotes.

In **prokaryotes**, **initiation complex** includes Initiator tRNA charged with N-formylmethionine (fMet) - Small ribosomal subunit - mRNA strand

- Ribosome binding sequence (RBS) of mRNA positions small subunit correctly.

- Large subunit now added.

- Initiator tRNA bound to P site with A site empty.

Translation (cont)

Initiations in *eukaryotes* similar except:

- Initiating amino acid is **methionine**.
- **Lack** of an RBS – small subunit binds to *5' cap* of mRNA.

Elongation adds amino acids

- 2nd charged tRNA can bind to empty A site
- Requires elongation factor called EF-Tu to bind to tRNA and GTP
- Peptide bond can then form.
- Addition of successive amino acids occurs as a cycle.

- There are fewer tRNAs than codons
- **Wobble** pairing allows less stringent pairing between the *3' base of the codon* and the *5' base of the anticodon*
- This allows fewer tRNAs to accommodate all codons

Termination

- Elongation continues until the ribosome encounters a *stop codon*
- Stop codons are recognized by *release factors* which release the polypeptide from the ribosome



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