Chem 150, Spring 2015

Unit 13 - Nucleic Acids and Protein Synthesis

Introduction

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  - High levels are an indication that the infant has a genetic disease called **phenylketonuria (PKU)**.

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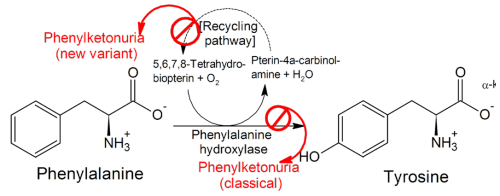

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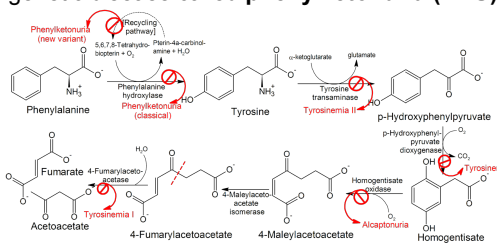

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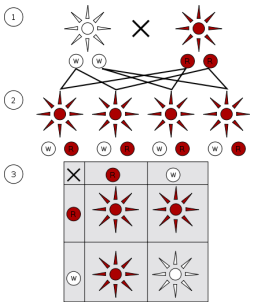
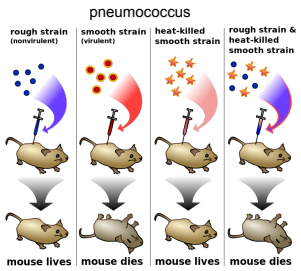


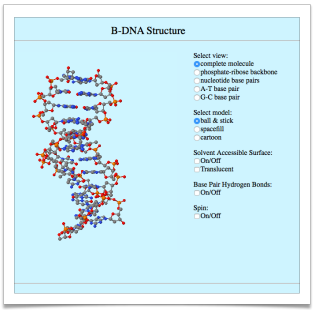
Introduction

- Nucleic acid were discover in 1800's, but it was not until the 1940's that their significance was appreciated.



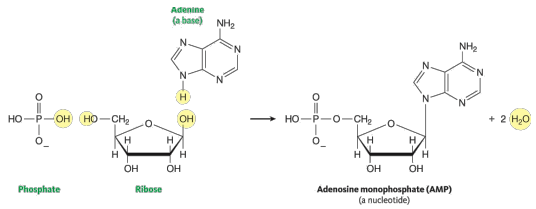
Introduction

- Less than 10 years later, in 1953, Francis Crick and James Watson determined a structure for DNA.

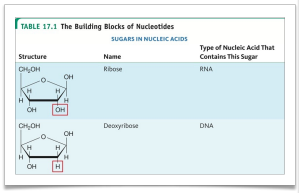


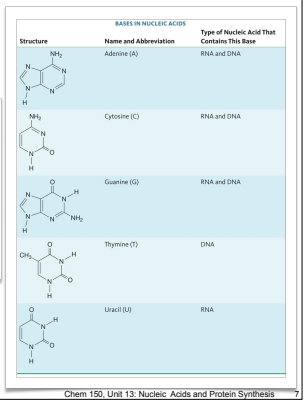
17.1 Nucleotides

- Nucleic acids: Ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) were discovered to carry genetic information in 1944.
- Nucleotides are the building blocks of nucleic acids.
  - All nucleotides contain a phosphate group, a five carbon sugar and an organic base.



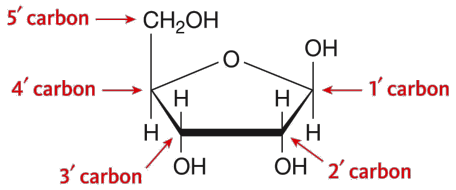
Building Blocks of Nucleotides



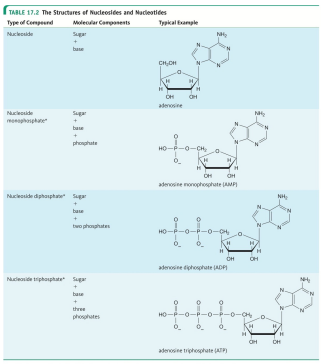


Other Features of Nucleotides

- The five carbon sugars of nucleotides are numbered like all sugars, except they are labeled as primes.



Nucleotides and Related Compounds



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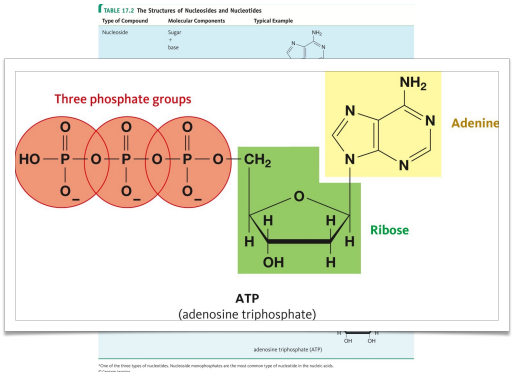

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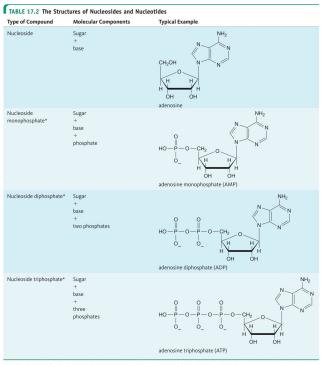
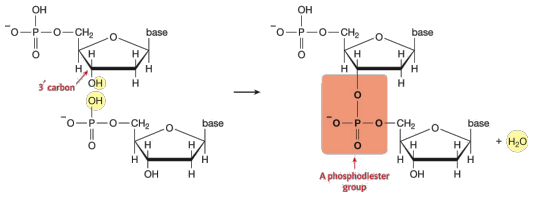


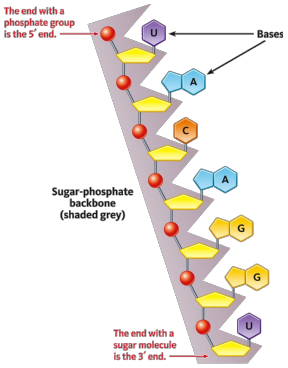
17.2 The Structure Nucleic Acids

- DNA and RNA are chains of nucleotides.
  - The OH on the 3' carbon of one sugar condenses with the phosphate group on the 5' carbon of another sugar, forming a phosphodiester group.



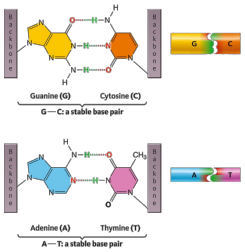
Backbone

- The phosphate-sugar bonds form the backbone of DNA, with a free phosphate group on the 5' end and a sugar on the 3' end.



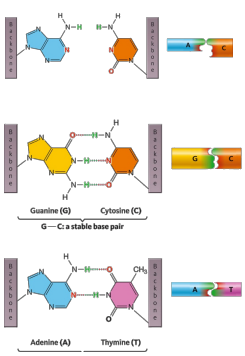
Bases Form Complementary Pairs

- In double-stranded DNA, complementary base pairs form hydrogen bonds
- Guanine forms 3 hydrogen bonds with Cytosine.
- Adenine forms 2 hydrogen bonds with Thymine



Bases Form Complementary Pairs

- Complementary base pairs form hydrogen bonds, a very important feature in DNA and RNA.
- Missmatched nucleotides, such A with C, cannot hydrogen bond.



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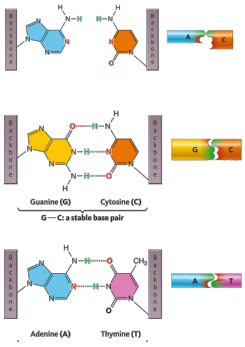
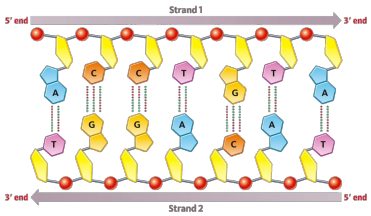


Double Stranded DNA

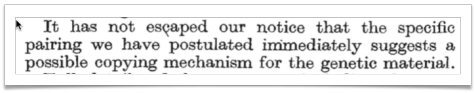
- DNA is arranged by two strands going in opposite directions and held together by base pairing.



Try It!

Question:

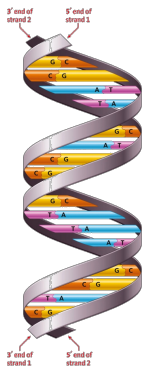
When Watson and Crick proposed their model for double-stranded DNA, it was immediately accepted because it could explain how the DNA could be duplicated during cell division? What is the explanation?



It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.

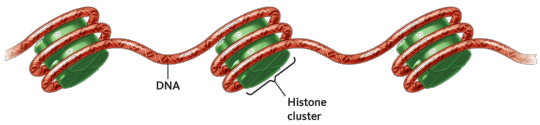
Double Helix

- The two strands of DNA coil to form a double helix, with the hydrophobic base pairs in the middle and the hydrophilic backbone exposed.
- For humans, all of our genetic information is contained in 46 strands of DNA (23 from your mother and 23 from your father), making DNA molecules very large.



Chromosomes

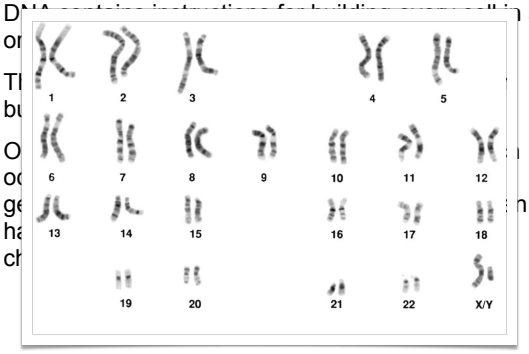
- In eukaryotes, DNA is primarily housed in the nucleus.
- To fit the large DNA molecules, the double helix of DNA wraps around proteins called histones, which also coil with other proteins, forming a compact mass known as a chromosome.



17.3 DNA Replication

- DNA contains instructions for building every cell in an organism.
- The sequence of bases of DNA is instructions for building proteins.
- Of the 46 chromosomes, 44 are autosomal, which occur in pairs containing the same collection of genes and 2 are sex chromosomes, X and Y. Men have one X and one Y, women have two X chromosomes.

17.3 DNA Replication



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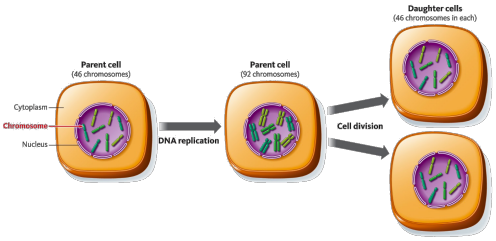
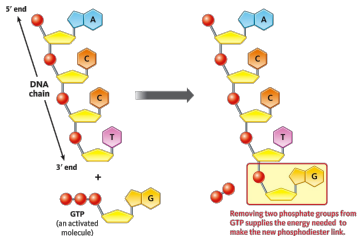
Cell Division

- Daughter cells will end up with a full set of chromosomes, which contain all genetic information and is known as the genome.



Replication

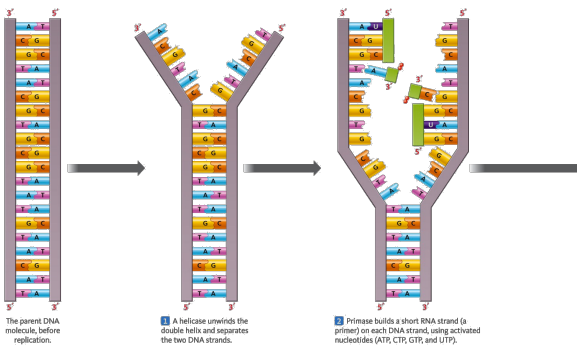
- Cells copy DNA through replication. A cell needs a supply of nucleoside triphosphates (dATP, dGTP, dCTP, and dTTP: called activated nucleotides) to build new DNA copies.
- Removing two phosphate groups as a base is added to a DNA chain provides energy for the process.



Four Steps of Replication

1. Helicase (a protein) pulls the DNA strands apart.
2. Primase (an enzyme) builds short RNA strands (primers) on each DNA strand using activated RNA nucleotides (ATP, CTP, GTP and UTP)
3. DNA Polymerase (an enzyme) starts making DNA by adding activated DNA nucleotides to the primers until a full copy is made of each side, forming two chains of DNA, each containing an original DNA strand and a new DNA strand.
4. Because DNA replication starts in several areas at once, DNA ligase (an enzyme) converts RNA primers to DNA and seals the gaps.

Mechanism of DNA Replication



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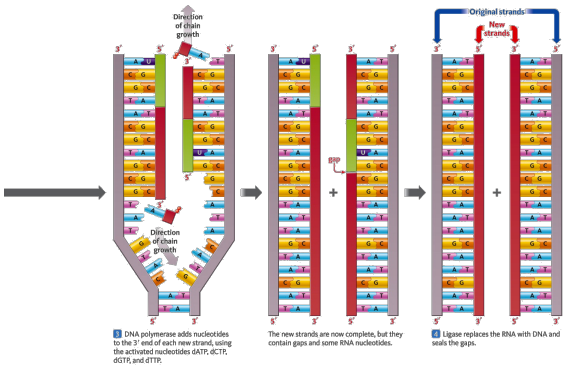
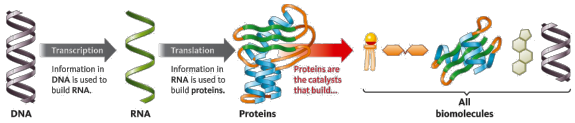


Mistakes in Replication

- A proofreading enzyme in DNA polymerase (which is actually a cluster of proteins) recognizes and corrects any mismatched base pairs.
- Proofreading catches 99% of errors, leaving one mistake per 10 million bases.
- Any mistake that is not corrected becomes a permanent part of the genome.

17.4 Transcription and RNA Processing

- DNA contains all of the information for a cell to make proteins.
- DNA is transcribed into RNA
  - Transcription: Think of this as being in the same language, that of bases.
- RNA is translated into proteins
  - Translation: Think of this as being in a new language, bases are translated to amino acids.



Types of RNA

- Messenger RNA (mRNA): a set of instructions for proteins
- Transfer RNA (tRNA): matches coded information of mRNA with the correct amino acid
- Ribosomal RNA (rRNA): a catalyst that utilizes mRNA and tRNA to allow amino acids to form a polypeptide chain.

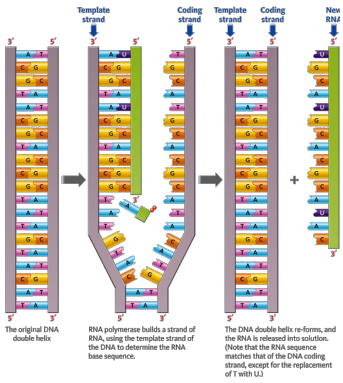
Transcription

- Transcription is similar to replication, except that only a single strand of RNA is made and only short sequences of DNA are copied.

1. Helicase unwinds a portion of the DNA. The portion that is selected is a gene.
2. RNA polymerase builds a strand of RNA complementing one side of the DNA, known as the template strand. The side that is not copied is the coding strand.

Transcription Continued

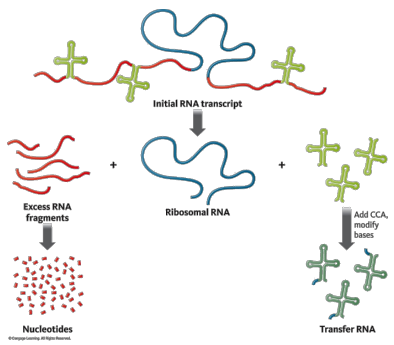
3. The DNA double helix re-forms, and the RNA strand (known as the initial transcript) is released. This RNA strand is identical to the DNA coding strand, except that it uses U instead of T.



Initial Transcript Modification

1. Ribosomal RNA contains extra bases that the cell must clipped out by enzymes.
2. Transfer RNA is also clipped out and modified by adding CCA to the 3' end and undergoes some base modification.
3. Messenger RNA:
   - capped at the 5' end to tag it as mRNA.
   - Some 3' bases are removed and a chain of adenine (Poly-A tail) is added to extend the life of the mRNA
   - **Introns** are clipped out, leaving only **exons**.

RNA Modifications



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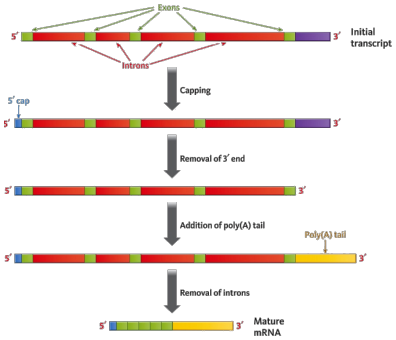

Introns and Non-coding DNA

- Introns are regions of DNA that do not code for any amino acid sequence.
- An estimated 98% of our DNA does not code for proteins. Approximately 1/3 of this DNA codes for tRNA, rRNA, introns and other small RNA whose roles are unclear.
- The remaining 2/3 of the non-coding DNA is apparently never transcribed and continues to be a source of mystery.

17.5 Translation and the Genetic Code

- mRNA contains a copy of a gene (the code for a single protein)

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- mRNA contains a copy of a gene (the code for a single protein)
- A sequence of three bases of mRNA corresponds to one amino acid. This sequence is known as a codon. In virtually all organisms, these codons translate in the same way.
- This genetic code contains 64 possible codons:
  - Some correspond to the same amino acid, one is a start codon (indicating where translation begins) and several are stop codons or nonsense codons (signaling where translation stops)

The Genetic Code

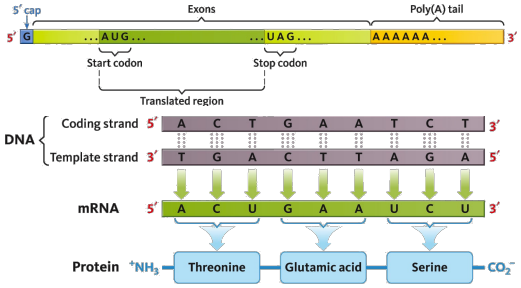
TABLE 17.3 The Genetic Code

FIRST POSITION (5′ END)	SECOND POSITION A	C	G	U
A	AAA = Lys	ACA = Thr	AGA = Arg	AUA = Ile
	AAC = Asn	ACC = Thr	AGC = Ser	AUC = Ile
	AAG = Lys	ACG = Thr	AGG = Arg	AUG = Met/start
	AAU = Asn	ACU = Thr	AGU = Ser	AUU = Ile
C	CAA = Gln	CCA = Pro	CGA = Arg	CUA = Leu
	CAC = His	CCC = Pro	CGC = Arg	CUC = Leu
	CAG = Gln	CCG = Pro	CGG = Arg	CUG = Leu
	CAU = His	CCU = Pro	CGU = Arg	CUU = Leu
G	GAA = Glu	GCA = Ala	GGA = Gly	GUA = Val
	GAC = Asp	GCC = Ala	GGC = Gly	GUC = Val
	GAG = Glu	GCG = Ala	GGG = Gly	GUG = Val
	GAU = Asp	GCU = Ala	GGU = Gly	GUU = Val
U	UAA = stop	UCA = Ser	UGA = stop	UUA = Leu
	UAC = Tyr	UCC = Ser	UGC = Cys	UUC = Phe
	UAG = stop	UCG = Ser	UGG = Trp	UUG = Leu
	UAU = Tyr	UCU = Ser	UGU = Cys	UUU = Phe

The start codon is shown in green, and the stop codons are in red.

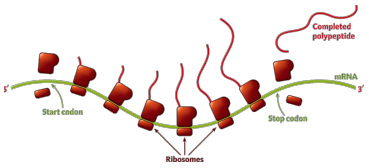
Building Proteins

- Cells build proteins from the N-terminus to the C-terminus using the information from codons. The coding strand and the mRNA are written 5' to 3'.



17.6 The Mechanism of Protein Synthesis

- mRNA is made in the nucleus and transported into the cytoplasm. Ribosomes, made up of rRNA and proteins, bind to the mRNA in the cytoplasm.
- The ribosome locates the start codon and forms a polypeptide as it moves toward the 3' end, releasing the mRNA and polypeptide at a stop codon.
- Several ribosomes bind at once forming several polypeptides simultaneously.



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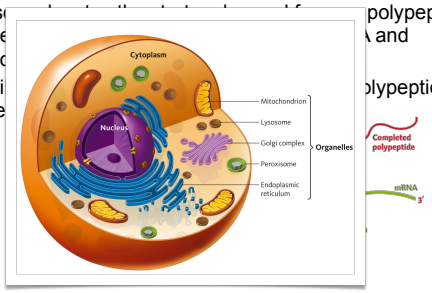

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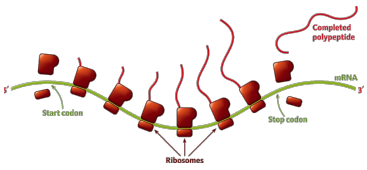
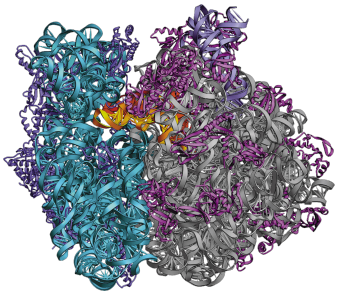


Ribosomes

- Molecular weight of 3,200,000 g/mole
- 60% rRNA and 40% protein



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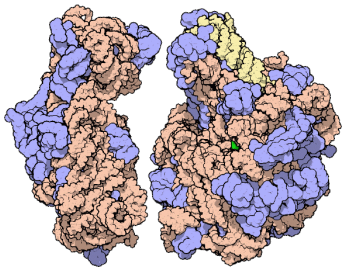

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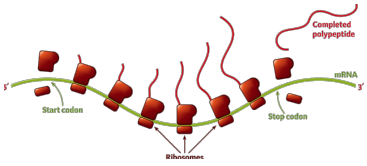
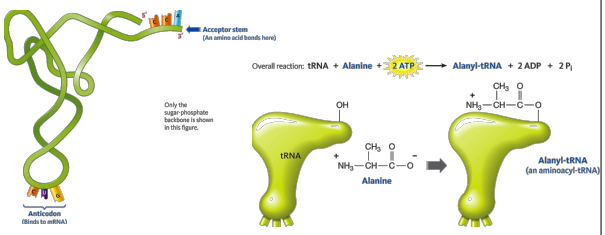


The Role of tRNA

- tRNA is an L-shaped molecules with two critical regions:
  - The anticodon, a three base sequence which complements the mRNA codon
  - The acceptor stem, the end of the tRNA that is bonded to the corresponding amino acid of the codon.
- The third base of the anticodon does not have to be an exact match. For instance, the AAU anticodon matches both UUA and UUG, both of which code for leucine. Therefore, there are fewer tRNA types than you might suspect.

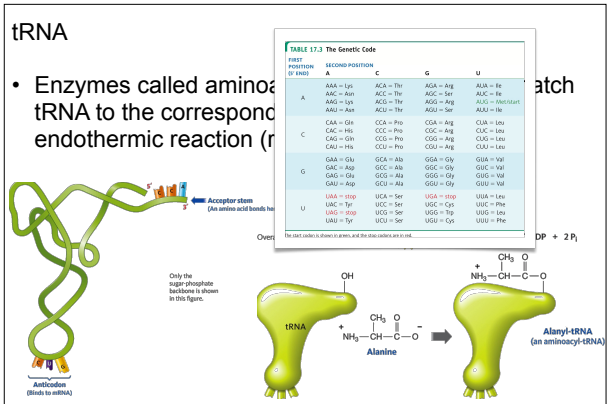
tRNA

- Enzymes called aminoacyl-tRNA synthetases match tRNA to the corresponding amino acid in an endothermic reaction (requires ATP).



tRNA

- Enzymes called aminoa…atch tRNA to the correspond… endothermic reaction (r…



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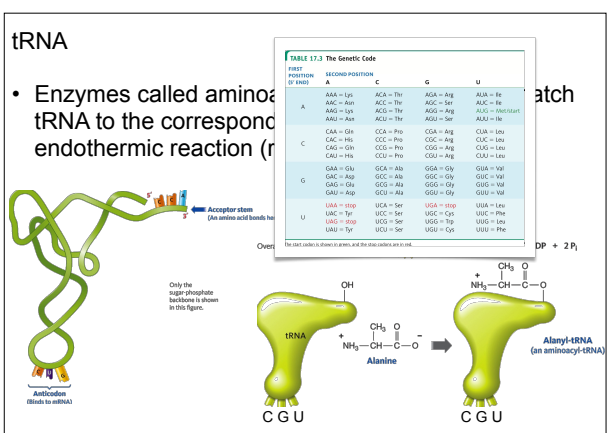
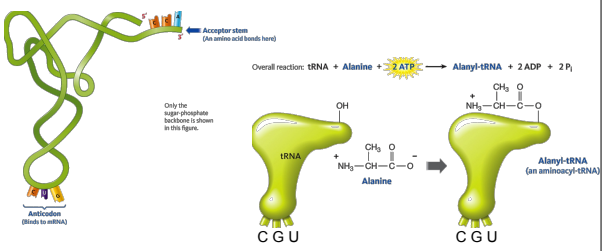


tRNA

- Enzymes called aminoacyl-tRNA synthetases match tRNA to the corresponding amino acid in an endothermic reaction (requires ATP).

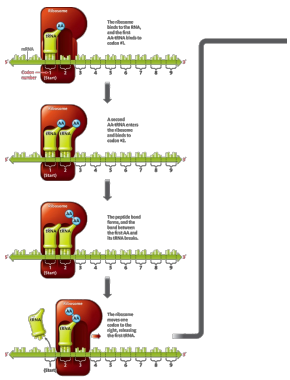


Translation

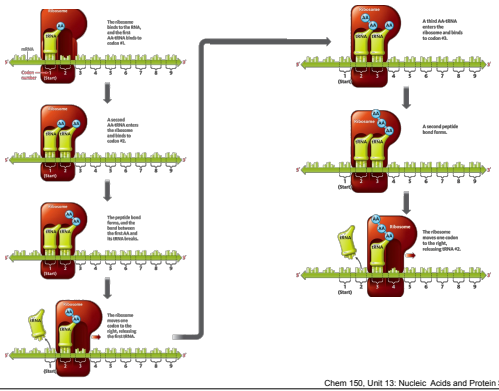
- During translation, two tRNA molecules bind to the mRNA based on the codons.
- A peptide bond forms between the amino acids of the tRNA molecules.
- The ribosome moves down the mRNA, allowing one tRNA to exit and a new tRNA to bind.
- This continues and the polypeptide grows larger until a stop codon signals the end of the chain.

Mechanism of Translation

Mechanism of Translation



Mechanism of Translation



The Energetic Costs

- It is estimated that more than half of the ATP that is produced by our bodies goes into building proteins.
  - Each amino acid added to a polypeptide costs the equivalent of 4 ATP molecules (due to the costs of activating each amino acid and on the cost of positioning tRNA on the ribosome)
  - Addition of each nucleotide in mRNA costs the equivalent of 2 molecules of ATP, though each mRNA is translated many times.

17.7 Mutations and Genetic Disorders

- Permanent changes of DNA that are passed from parent to offspring are known as mutations.
- Substitution mutations replace one base pair of DNA with another. There are 3 types:
  1. Silent Mutation: the mutated codon and the original codon code for the same amino acid. This has no effect on the protein formed or the cell.
  2. Nonsense Mutation: the original codon is converted to a stop codon. This causes the formation of short and typically inactive proteins. Nonsense mutations can be lethal to the cell.

Substitution Mutations Continues

- Substitution mutations:
  3. Missense Mutation: the mutated codon and the original codon code for different amino acids. This may or may not effect the function of the protein. If the different amino acids are similar to each other (like replacing leucine with isoleucine) the protein structure and function may not be changed.

     Missense mutations may also turn a stop codon into a meaningful codon, resulting in the formation of a longer protein that will typically be inactive.

Substitution Mutations Continues

- Substitution mutations:
  3. Missens
     original
     may or
     different
     replacing
     and func
     Missen
     a meani
     longer p

TABLE 17.3 The Genetic Code

FIRST POSITION (5′ END)	SECOND POSITION A	C	G	U
A	AAA = Lys	ACA = Thr	AGA = Arg	AUA = Ile
	AAC = Asn	ACC = Thr	AGC = Ser	AUC = Ile
	AAG = Lys	ACG = Thr	AGG = Arg	AUG = Met/start
	AAU = Asn	ACU = Thr	AGU = Ser	AUU = Ile
C	CAA = Gln	CCA = Pro	CGA = Arg	CUA = Leu
	CAC = His	CCC = Pro	CGC = Arg	CUC = Leu
	CAG = Gln	CCG = Pro	CGG = Arg	CUG = Leu
	CAU = His	CCU = Pro	CGU = Arg	CUU = Leu
G	GAA = Glu	GCA = Ala	GGA = Gly	GUA = Val
	GAC = Asp	GCC = Ala	GGC = Gly	GUC = Val
	GAG = Glu	GCG = Ala	GGG = Gly	GUG = Val
	GAU = Asp	GCU = Ala	GGU = Gly	GUU = Val
U	UAA = stop	UCA = Ser	UGA = stop	UUA = Leu
	UAC = Tyr	UCC = Ser	UGC = Cys	UUC = Phe
	UAG = stop	UCG = Ser	UGG = Trp	UUG = Leu
	UAU = Tyr	UCU = Ser	UGU = Cys	UUU = Phe

The start codon is shown in green, and the stop codons are in red.

Substitution Mutations Continues

- Substitution mutations:
  3. Missense Mutation: the mutated codon and the original codon code for different amino acids. This may or may not effect the function of the protein. If the different amino acids are similar to each other (like replacing leucine with isoleucine) the protein structure and function may not be changed.

     Missense mutations may also turn a stop codon into a meaningful codon, resulting in the formation of a longer protein that will typically be inactive.

Examples of Substitution Mutations

TABLE 17.4 The Three Types of Substitution Mutations

Original DNA (Coding Strand)	Mutation	Type of Mutation	Mutated DNA (Coding Strand)*	mRNA	Amino Acid	Result of Mutation
TTA (codes for leucine)	Change base 3 from A to G	Silent	TT**G**	UUG	Leucine	The amino acid sequence is unchanged.
	Change base 1 from T to A	Missense	**A**TA	AUA	Isoleucine	Isoleucine is substituted for leucine.
	Change base 2 from T to A	Nonsense	T**A**A	UAA	None (stop codon)	The protein lacks some amino acids.

*The incorrect base is shown in red.

Addition and Deletion Mutations

- Addition Mutations: one or more base pairs is inserted into the DNA.
- Deletion Mutations: one or more base pairs is removed from the DNA.
- Both of these normally cause a frameshift, in which all codons following the mutation are translated incorrectly.
- This normally results in an inactive protein.

Implications

Original coding strand: ACG ATC ATT ACG

mRNA is: ACG AUC AUU ACG

corresponding to: Thr Ile Ile Thr

Implications

Original coding strand: ACG ATC ATT ACG

mRNA is: ACG AUC AUU ACG

corresponding to: Thr Ile Ile Thr

An addition mutation: ATC GAT CAT TAC G

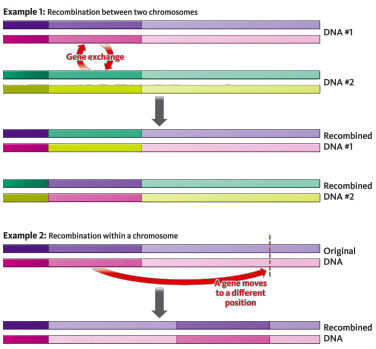
mRNA is: AUC GAU CAU UAC G

Corresponding to: Ile Asp His Tyr

Recombination Mutations

- In recombination mutations, a large section of DNA moves from one DNA molecule to another.
- If the recombination disrupts a gene, there may be devastating effects on the cell.
- Cells can use recombination to replace damaged DNA, a process common in bacteria.
- When recombination moves an entire gene to another chromosome, this creates genetic diversity by creating a new combination of genetic traits.

Two Types of Recombination



Chemicals and Radiation

TABLE 17.6 Chemicals and Radiation That Cause Mutations

Mutagen	Source or Use	Effect
Nitrosamines	Formed when meats containing nitrites are cooked	Modify the structures of C and G, producing substitution mutations
Acridine orange	Used as a dye to detect bacteria	Inserts between bases in the double helix, producing insertion mutations
Temozolomide	Used as a medication in the treatment of brain tumors	Adds methyl groups to DNA bases, producing substitution mutations
2-Amino-1-methyl-6-phenylimidazo[4,5-b] pyridine (PhIP)	Formed during cooking of foods containing protein	Combines with G, producing substitution mutations
Benzo[*a*]pyrene	Formed as a component of smoke from cigarettes, fireplaces, barbecues, etc.	Combines with G, producing substitution mutations
Aflatoxin B_1	Formed by molds that grow on certain food crops	Combines with DNA bases to produce substitution mutations and appears to increase recombination rates
Ultraviolet radiation	A component of sunlight	Forms covalent bonds between adjacent Ts, producing a variety of errors in replication
X-rays	Used for diagnostic imaging in medicine (including CT scans)	Produce a range of chemical changes in DNA
Gamma rays	Formed by radioactive elements and used in some cancer treatments	Produce a range of chemical changes in DNA

Devastating Mutations

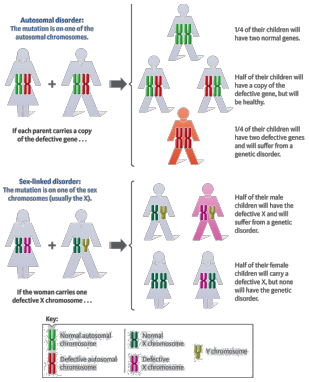
- Most single mutations within a single cell may be devastating to that cell, but typically don't effect the health of an organism overall.
- There are three instances of mutation that have enormous impact on an organism:
  1. **The mutation damages the DNA that controls cell division**. If cell division spirals out of control (which is caused by several mutations in key areas), the result is cancer.
  2. **The mutation occurs in early stages of embryonic development.** Each embryonic cell is the precursor to many adult cells, and a mutation at this stage often causes embryo death.

Devastating Mutations

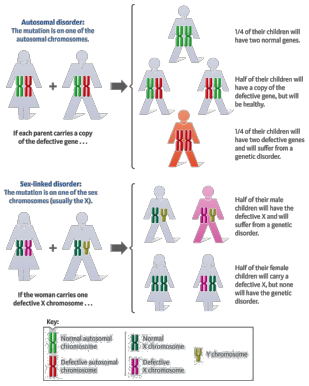
3. **The mutation occurs in an egg or sperm cell before fertilization.** Any mutation in either of these will be passed onto the embryo, and into every cell of the person who develops from the fertilized egg.

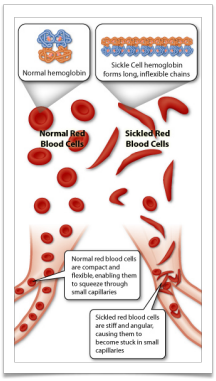
- A mutation in an autosomal chromosome may have no ill effects on an individual, as everyone inherits two of each of the autosomal chromosomes.
- Autosomal and sex-linked genetic disorders result when one or both parents carry a mutated autosomal or sex-linked chromosome.

Autosomal and Sex-Linked Disorders

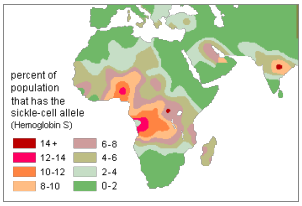


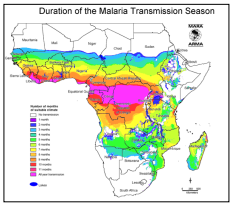
Autosomal and Sex-Linked Disorders





Autosomal and Sex-Linked Disorders





Next Up

- Final Exam
  - Tuesday, 19. May, 8:00am in Phillips 007.