F. Mutation and Repair

1. Background on DNA Mutations
2. Common Types and Mechanisms of DNA Damage, Mutation and Repair

1. Background on DNA Mutations

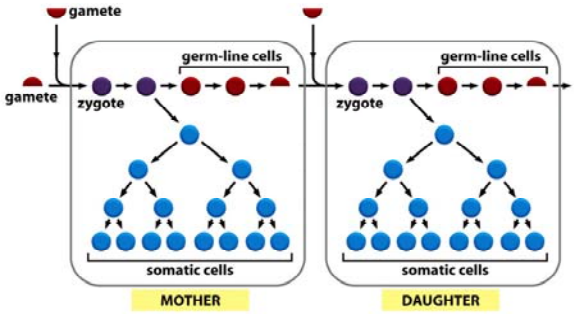
a. Mutation rates are extremely low but are an essential component of evolutionary change

b. The most common source of DNA mutation is error during replication

c. Environmental damage to the DNA is independent of DNA mutation but can also be the underlying cause

a. Mutation rates are extremely low but are an essential component of evolutionary change

- Mutations that become part of the multicellular genome must occur in the cells of the germ line
- Somatic mutations may or may not affect the individual but cannot affect the population
- Low rates of mutation can result in high rates of evolution in single-celled organisms



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b. The most common source of DNA mutation is error during replication

- There is an average mistake of 1 base pair every 10,000
- Due to proofreading and repair mechanisms this rate declines to 1 every 1,000,000,000
- Inherent in meiosis are assortment and cross-over events that lead to highly significant changes in germ line DNA sequences

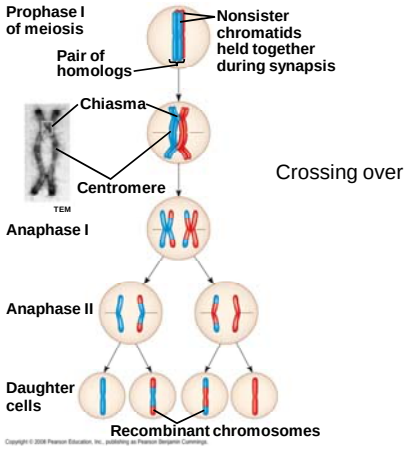
Independent Assortment of Chromosomes

- Homologous pairs of chromosomes orient randomly at metaphase I of meiosis
- In independent assortment, each pair of chromosomes sorts maternal and paternal homologues into daughter cells independently of the other pairs
- The number of combinations possible when chromosomes assort independently into gametes is 2^n, where n is the haploid number
- For humans (n = 23), there are more than 8 million (2^{23}) possible combinations of chromosomes

Random Fertilization

- Random fertilization adds to genetic variation because any sperm can fuse with any ovum (unfertilized egg)
- The fusion of two gametes (each with 8.4 million possible chromosome combinations from independent assortment) produces a zygote with any of about 70 trillion diploid combinations

Fig. 13-12-5



Crossing Over

- Crossing over produces **recombinant chromosomes**, which combine genes inherited from each parent
- Crossing over begins very early in prophase I, as homologous chromosomes pair up gene by gene
- In crossing over, homologous portions of two nonsister chromatids trade places
- Crossing over contributes to genetic variation by combining DNA from two parents into a single chromosome

c. Environmental damage to the DNA is independent of DNA mutation but can also be the underlying cause

1. DNA damage is simply a chemical alteration to DNA, whereas DNA mutation is a change in one or more base pairs
2. DNA damage becomes DNA mutation when DNA replication proceeds without repairing the damage or by means of error-prone DNA repair systems

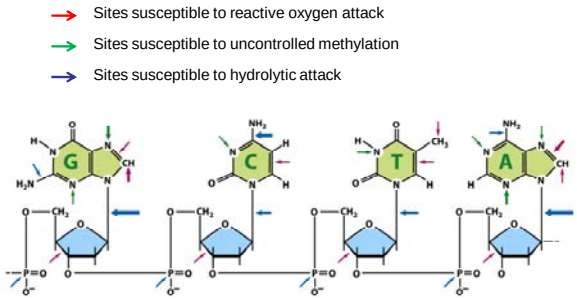
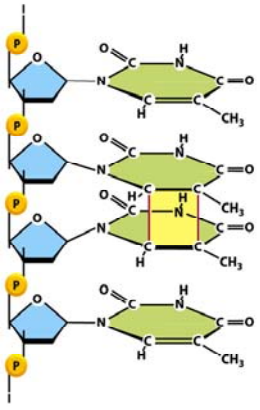


Figure 5-44 *Molecular Biology of the Cell* (© Garland Science 2008)



UV radiation can lead to dimerization between adjacent pyrimidine bases

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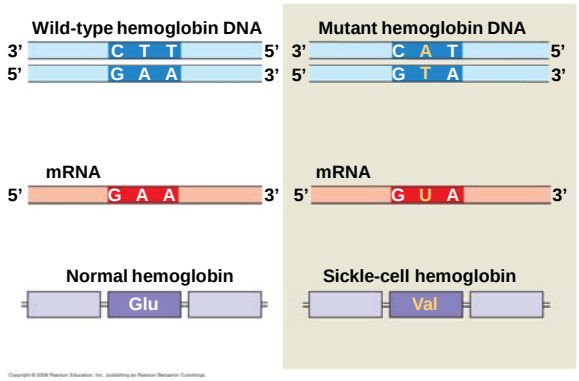
Fig. 17-2

Example Mutation: Sickle Cell Anemia



2. Common Types and Mechanisms of DNA Damage, Mutation and Repair

a. The alteration of a single base pair (point mutation) can result from chemical damage followed by copying error

b. The insertion or deletion of a single base pair (point mutation) during DNA replication

c. Single-stranded and double-stranded breaks can result from electrophilic attack from reactive oxygen species

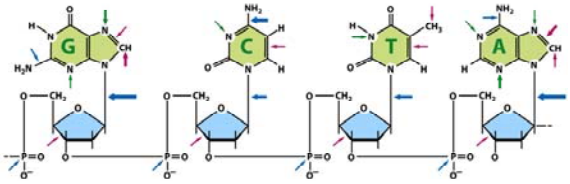
a. The alteration of a single base pair (point mutation) can result from chemical damage followed by copying error

1. DNA damage leading to structural distortion of the base pair chemistry
2. DNA base pair changes (mutations) that result from structural distortion can include transitions and transversions
3. Potential outcomes in protein expression and phenotype
4. Several DNA repair systems can remove these mutations

1. DNA damage leading to structural distortion

a. Alkylation of nitrogen in bases
b. Deamination of cytosine to form uracil
c. Formation of pyrimidine dimers

Sites susceptible to reactive oxygen attack
Sites susceptible to uncontrolled methylation
Sites susceptible to hydrolytic attack



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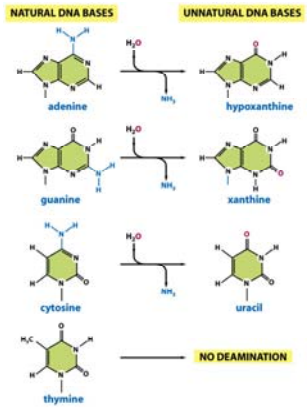


Figure 5-50a *Molecular Biology of the Cell* (© Garland Science 2008)

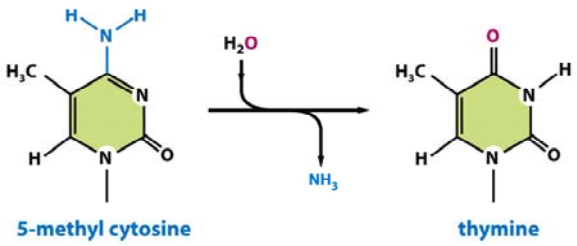
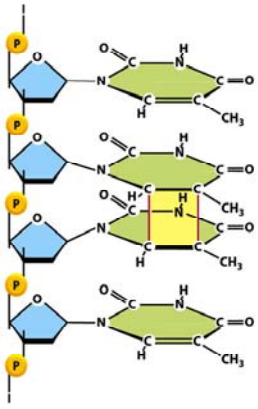


Figure 5-50b *Molecular Biology of the Cell* (© Garland Science 2008)



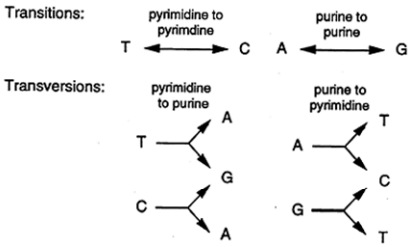
UV radiation can lead to dimerization between adjacent pyrimidine bases

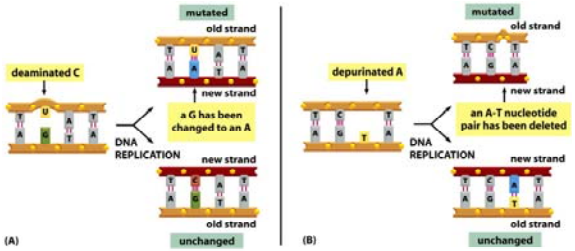
Figure 5-46 *Molecular Biology of the Cell* (© Garland Science 2008)

2. DNA base pair changes (mutations) that result from structural distortion

a. Transitions: Change from a pyrimidine to another pyrimidine or change from a purine to another purine. Causes mismatch.

b. Transversion: change from a purine to a pyrimidine or a pyrimidine to a purine. Also causes mismatch.





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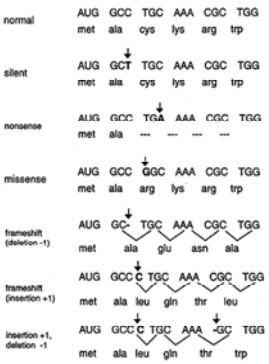
3. Potential outcomes in protein expression and phenotype

a. **Silent mutations** have no effect on the amino acid produced because of redundancy

b. **Missense mutations** still code for an amino acid, but not necessarily the right amino acid

c. **Nonsense mutations** change an amino acid codon into a stop codon, nearly always leading to a nonfunctional protein

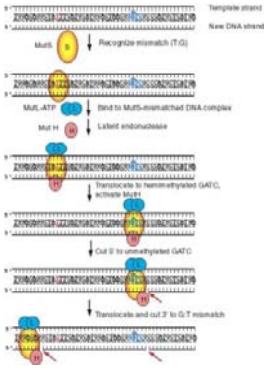
d. Insertion or deletion of nucleotides may alter the reading frame, producing a **frameshift mutation**



4. Several DNA repair systems can remove these mutations

   a. Mismatch repair
   b. Base excision repair
   c. Nuclear excision repair

Mismatch Repair



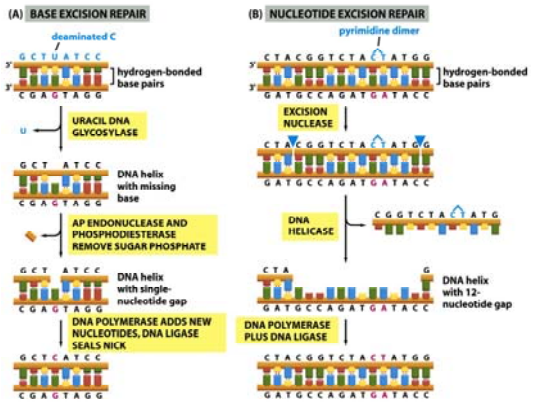
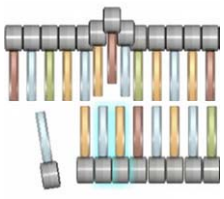


Figure 5-48 *Molecular Biology of the Cell* (© Garland Science 2008)

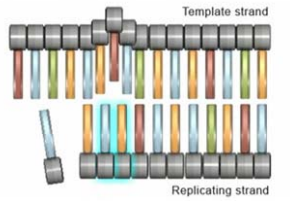
b. The insertion or deletion of a single base pair (point mutation) during DNA replication

1. One of two steps in replication can produce error: mistaken reading of template and/or addition of base to daughter strand by DNA Polymerase
2. Frame shift mutation is the result
3. Potential outcomes in protein expression and phenotype
4. Several DNA repair systems can remove these mutations

1. One of two steps in replication can produce error: mistaken reading of template and/or addition of base to daughter strand by DNA Polymerase

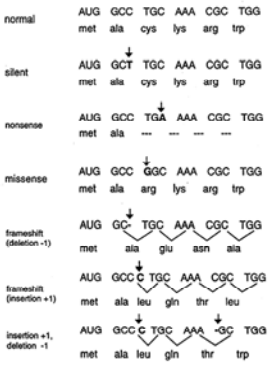


deletion



insertion

2. Frame shift mutation is the result



3. Potential outcomes in protein expression and phenotype

a. Silent mutations if out of reading frame
b. Functions lost downstream
c. Nonsense mutations change an amino acid codon into a stop codon, nearly always leading to a nonfunctional protein

4. Several DNA repair systems can remove these mutations

a. Mismatch repair
b. Base excision repair
c. Nuclear excision repair

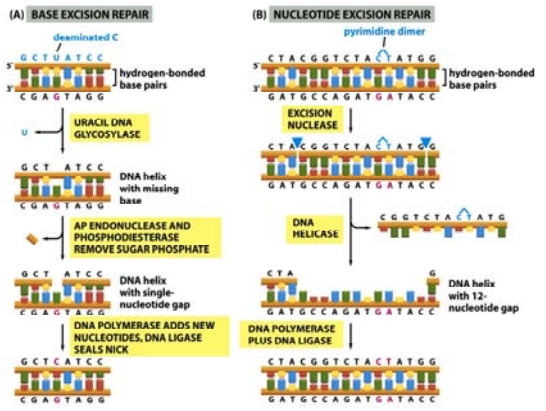
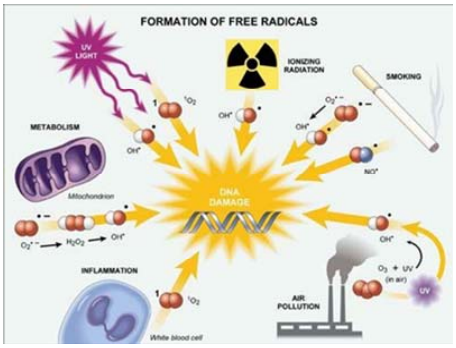


Figure 5-48 *Molecular Biology of the Cell* (© Garland Science 2008)

c. Single-stranded and double-stranded breaks can result from reactive oxygen species activity

1. ROS are generated by either endogenous metabolic processes or exogenous ionizing radiation (like gamma and X-rays)
2. DNA mutation is the loss or gain of significant amounts of DNA, including chromosomal deletions, additions
3. Potential outcomes range from gene shuffling in or across chromosomes, gene inactivation, altered gene regulation, gene duplication
4. DNA repair system that can remove these mutations

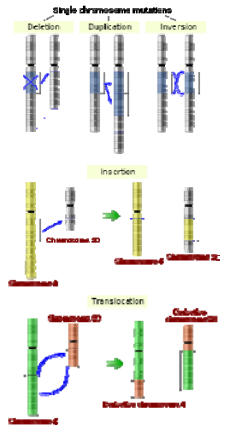
1. ROS are generated by either endogenous metabolic processes or exogenous ionizing radiation (like gamma and X-rays)



2. DNA mutation is the loss or gain of significant amounts of DNA, including chromosomal deletions, additions

a. Insertion: addition of variable sized nucleotide fragment

b. Deletion: deletion of variable sized nucleotide fragment



3. Potential outcomes range from gene shuffling in or across chromosomes, gene inactivation, altered gene regulation, gene duplication

a. Double stranded breaks can drift apart and religate with other chromosomes

b. Regions of microhomology can match up and reanneal to rejoin the two broken ends. This causes hypermutation because some DNA is lost.

4. DNA repair system that can remove these mutations

   a. Nonhomologous End-Joining
   b. Homologous End-Joining

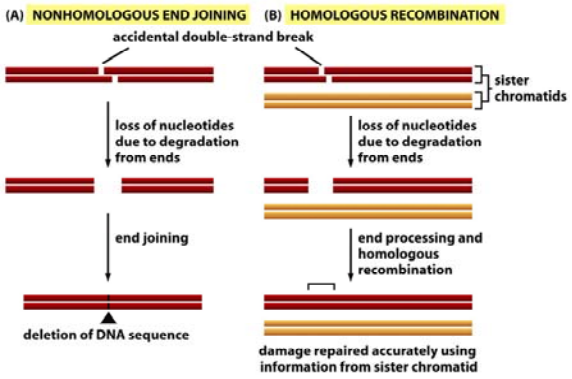


Figure 5-51 *Molecular Biology of the Cell* (© Garland Science 2008)

Gene conservation is the maintenance of DNA sequences across species.

If the function is essential and unchanged, the structure (sequence) is unchanged.

If it's a protein function you've got to have, you must repair any mutations or you're toast

Fundamental activities, such as sequences for ribosome expression, are much the same in all cells

Gene duplication and gene families define the advancing complexity of living organisms.

1. The idea is that during meiosis in sexually reproducing organisms, crossover mutations can form multiple copies of a gene, a chromosome or the entire genome.
2. The organism survived just fine with one copy so it only repairs damages (mutations) to one copy, leaving the other to freely mutate.
3. Once in a blue moon the mutated copy develops new, advantageous functions.