Genetics Notes Chapter 16: Mutation, Repair, and Recombination

16.1-The Phenotypic Consequences of Gene Mutations

- **Point Mutation**-Alteration of a specific base pair or small number of adjacent base pairs.
- Two main types of point mutations:
    - **Base Substitutions**-One base substitute in for another. Two types:
        - **Transistion**- A purine is replaced by a purine or a pyrimidine is replaced by a pyrimidine.
        - **Transversion**-A purine is replaced by a pyrimidine and vice-versa.
    - **Base Insertions and Deletions**- The insertions or deletions of nucleotide pairs. Shortly called **indel mutations**.
- Three possible phenotypic effects of base-pair substitution:
    - **Synonymous mutation**-The base pair substitution changes the codon that codes for one amino acid to a different codon that codes for the same amino acid. Also referred to as **silent mutations** because they have no phenotypic effect.
    - **Missense mutation**- The codon for one amino acid is changed to a codon that codes for a different amino acid. Also called **nonsynonymous mutation**. Two types:
        - **Conservative substitution**-A missense mutation that codes for a chemically similar amino acid to the wildtype amino acid. Not likely to severely affect protein function.
        - **Nonconservative substitution**- A missense mutation that codes for a radically chemically different amino acid from the wildtype. More likely to have a severe change on protein structure and function.
    - **Nonsense Mutation**-A codon for an amino acid is changed into a stop codon. This normally results in early termination of the translation of the polypeptide. The closer it is to the 3' end of the reading frame the less likely it is to damage protein structure and function.
- Many mutations in proteins are due to splice site mutations that make the site unrecognizable to spliceosomes which then sometimes leave in large sections of introns in the final transcript.
- Insertion or Deletion mutations are often called **frameshift mutations** and usually result in the loss of function of the protein.
- Mutations also occur in nonprotein coding regions of the genome, although these are harder to spot.
- A mutation in the regulatory region of DNA can sometimes lead to no mRNA and therefore no protein production.

16.2-The Molecular Mechanisms of Spontaneous Mutations

- **Spontaneous mutations**-naturally occurring, arise in all cells.
- **Induced mutations**-arise through the action of certain agents called **mutagens**.
- Luria and Delbruck ran a test called the **"fluctuation test"** where they tested how E. coli cells gained their resistance to a certain phage.
- They saw that mutants occurred at random numbers in different cultures and so determined that this mutation was not induced by the bacteriophage but was instead random.
- Mutations are often caused by errors in DNA replication.

- Sometimes mispariring occurs and is not corrected by DNA Pol 3.
- Mismatches can be caused by the **ionization** of a base pair or the **tautomerization** of a base pair.
- There can also be **spontaneous lesions**-naturally occurring damage to DNA that results in mutation.
    - **Depurination**-the loss of a nitrogenous base from a purine nucleotide.
    - **Deamination**-the removal of an amine group from cytosine causing it to change to uracil. The uracil will bind with adenine causing a GC -> AT pair switch.
    - Mutations due to **oxidative damage**.
- A common mechanisms responsible for genetic diseases are **extensions** of three nucleotide sequences.
- Oftentimes, the more repeats of these 3-nucleotide sequence the more of the phenotype that is displayed.

16.3-The Molecular Basis of Induced Mutations

- **Mutagenesis**-The production of mutations in the laboratory through exposure to mutagens.
- Sometimes chemical compounds are so similar to nitrogenous bases that they are incorporated instead of the normal nucleotide. These are called **base analogs**. This can lead to mispairings and mutations that proliferate when the DNA is replicated.
- Some mutagens chemically alter the base by adding **alkyl groups** which leads to base mispairing and mutations.
- **Intercalating agents**- mimic bases and insert themselves into the DNA. They can cause indel mutations from there.
- Sometimes mutagens work by damaging the base which causes a block to DNA replication if not fixed. These types of mutagens include:
    - **Ultraviolet Light**
    - **Ionizing Radiation**-through creation of oxidative compounds and through direct damage to the DNA.
- The **Ames Test** is used today to screen compound for mutagenic and potentially carcinogenic properties.
- His- mutant bacterial cells are grown in ground up liver to simulate growth in a mammalian host organisms.
- These cells are exposed to the compound of interest and then plated on a minimal medium.
- If colonies grow, then that means that they were reverted back to wildtype through mutation.
- If mutation levels are abnormally high, then the compound is a potential mutagen/carcinogen.

16.4-Biological Repair Mechanisms

- The most straightforward way to repair a lesion is to reverse it and regenerate the normal bases.
- An example of this is the removal of a **mutagenic photodimer** called CPD that is caused by UV radiation. An enzyme called CPD photolyase comes in (and through power from light) splits the photodimer restoring the two bases. This process is called **photoreactivation**.
- **Alkyltransferases** are enzymes that remove alkyl groups from nitrogenous bases thereby unmutating them.

- **Homology-dependent repair systems** depend on the complementary nature of DNA bases to remove a mutated base and replace it with a new one based on the complementary strand.
- In **base-excision repair** after DNA Pol does its proofreading and recognizes a mistake **DNA glycolysase** comes in and cleave the nitrogen-base/sugar bond creating an apurinic/apyrimidinic area (no nitrogenous base), **AP endonuclease** then cuts the damaged strand upstream of the mutation, and then an enzyme called **dRpase** removes some neighboring nucleotides so the **DNA pol** can come in a synthesize a new section of strand which is sealed by **ligase**.
- **Uracil**-DNA glycosylase removes uracils that have been created through the deamination of cytosines. Can recognize this mutation because uracil is not normally in DNA.
- When large sections of DNA are damaged and replication or transcription cannot continue, cells utilize **nucleotide excision repair**.
- NER works by:
    - Recognizing damaged bases.
    - Assembling a multi-protein complex to the damaged site.
    - Cutting the damaged strand upstream and downstream of the site.
    - Using the template strand to replace the nucleotides and ligase to repair it.
- Two types of NER:
    - **Transcription-Coupled Nucleotide-Excision Repair**- for the transcribed regions of DNA.
    - **Global Genomic Repair**- corrects any genes in the genome.
- **Mis-match repair systems** are responsible for correcting whatever left over errors there may be. They function by:
    - Recognizing mismatched base pairs.
    - Determining which base pair is incorrect-The wrong base pair is always on the newly synthesized strand. Can distinguish the old strand from the new strand by the epigenetic methylation inherited onto the old strand and not yet added to the new strand.
    - Excising out the mismatched base and carrying on repair synthesis.
- In prokaryotes and eukaryotes some lesions can prevent the continuation of DNA replication, this sometimes causes cell death, but in other cases induces a cell **SOS system**. In the SOS system DNA continues to be unraveled past the replication fork when DNA Pol stalls. This causes a protein called **RecA** to call over different polymerases called **bypass polymerases**. These are able to continue replication past the lesion. This system is imperfect and often leads to mutation, but this is usually better than cell death.
- Sometimes mutagens cause **double-stranded DNA breaks** in which the complementarity of the DNA cannot be utilized in the DNA repair.
- One way of fixing this problem when no sister chromatids are available, is through non-homologous end joining. The broken edges are trimmed by enzymes until the 5' ends and 3'ends are exposed, these two new sites are then rejoined by ligase to prevent further damage.
- If a double stranded break occurs after DNA replication when sister chromatids are available then synthesis-dependent strand annealing can occur. Enzymes invade the undamaged sister chromatid and utilize that strand as a template for the damaged strand.

16.5-Cancer