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Lecture 8 (2/18/08)
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# DNA Mutability

I. DNA is the repository of genetic information for the cell and for the species. Mutations are a double edged sword; while they may be evolutionarily advantageous for the species, they are usually deleterious to the individual.

II. Structure of bases, nucleosides, nucleotides, and the polarity of DNA polymers all contribute to DNA mutability

III. Mutations and damage at the molecular level:

A. Base substitutions-->missense and nonsense mutations

B. Base insertions or deletions-->frameshift mutations

C. Large scale insertions and deletions--transposons and recombinational mutagenesis

D. DNA duplex structural damage--gross damage to the double helical structure

IV. Phenotypic consequences of mutations at the protein, cellular, and organismal level:

A. Conditionally advantageous (forward and reverse mutations)

B. Neutral

C. Conditionally deleterious

D. Deleterious

E. Lethal

V. Example of a deleterious base substitution: sickle cell anemia

VII. Mutations in non-coding sequences

VIII. Mechanisms of mutation and damage generation

A. Spontaneous--the baseline mutation rate

1. The chemistry of DNA, tautomeric forms and cytosine deamination

2. The inherent limitations of DNA polymerase-misincorporation and template slippage

3. "DNA mutases" -UmuCD', DinB, REV1, REV3/7, RAD30....

B. Induced--factors which increase the rate above baseline

1. Genetic factors: "Mutator" and "antimutator" genes-host mutations affecting proofreading and repair enzymes--the use of mutagenesis to study the pathways of repair

2. Environmental factors

a. Chemical mutagens, causing base substitutions

(1) alkylating agents

(2) nucleotide analogs

(3) deaminating agents

(4) intercalating agents

(5) drugs which alter the balance of nucleotide pools

b. Physical forces causing DNA damage

(1) UV light, causing modification of bases

(2) Oxygen free radicals, causing creation of apurinic and apyrimidinic sites

(3) Free radicals, electromagnetic radiation causing breakage of the DNA backbone leading to nicks or double stranded breaks.

c. The Ames test

C. Control of damage:

1. Inherent mechanisms

a. Redundancies in the genetic code lessen the effect of a given mutation

b. The double stranded nature of DNA provides an available template for repair

c. Diploidy means a duplicate copy of a gene or chromosome is available for recombinational repair

2. Specific genetic repair pathways

a. 3' to 5' exonucleases proofread the nascent DNA polymerase products

b. Post-replication repair mechanisms

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Readings:
Watson
Chapter 1, pp. 15-18
Chapter 6, pp. 98-102
Chapter 8, pp. 184-192
Chapter 9, pp. 236-258