

# ENVIRONMENTAL GENE INTERACTIONS

Genotoxins and Genetic Instability  
Lecture 10/20/09

TA: Kristin Yamada

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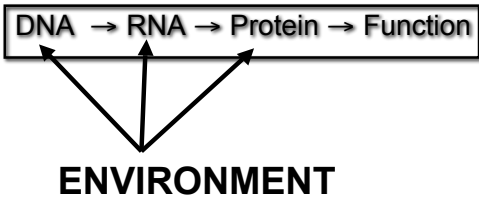
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## Central Dogma of Molecular Biology



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## Basics

- Purine: (A & G) 2 ring structure
- Pyrimidine (T & C & U) 1 ring structure
- Genotype: Gene sequence
- Phenotype: outward manifestation of gene like hair and eye color

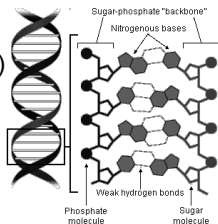


Image: <http://evolution.berkeley.edu/evosite/history/dna2.htm>  
Copyright 2006 by The University of California Museum of Paleontology, Berkeley, and the Regents of the University of California

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## Genetic Damage

- Clastagenic: structural damage to chromosomes
- Mutagens: change in DNA sequence
  - Transition: purine is exchanged with purine (A↔G) or pyrimidine is exchanged with pyrimidine (T↔C)
  - Transversion: purine is exchanged with pyrimidine (G↔C; T↔A; ionizing radiation)

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## Common mutations

- Dimerization (UV light)
- Alkylation of O6 on G (tobacco smoke)
- Alkylation of N7 on G (tobacco smoke)
- Attachments of bulky adducts to DNA (B(a)P)
  
- In general alkylation of O leads to mutations
- Whereas alkylation of N leads to chromosomal aberrations

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## Ames Test: test for mutagenesis

Steps:

1. Start with WT bacteria that can make its own histidine
2. Mutate it so it no longer can produce its own histidine
3. Expose to chemical
4. Grow in histidine deficient media
5. If Colonies multiply, a mutation has occurred

Histidine is an amino acid

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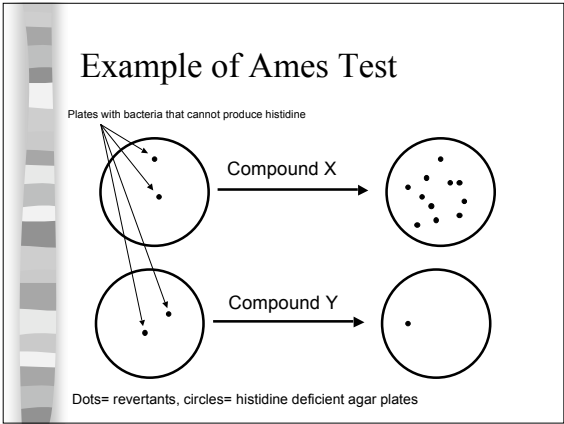
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- ### Protective Mechanisms
- Cell Cycle regulation
    - Check point mechanism, Nucleotide excision repair
  - Cell Death
    - Apoptosis (preferred, orderly suicide) and necrosis (messy! Triggers inflammation)

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- ### How does this relate to EHS?
- Chemicals and radiation in our environment can cause genetic damage
  - It is important to know what types of exposures cause each type of genetic damage
  - If there is damage or an insult to our protective mechanisms, it can be extremely harmful as you will see in carcinogenesis
  - The Ames test is a screening test used by pharmaceuticals and regulatory agencies

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# CANCER & CARCINOGENS

The central role of environmental injury in understanding the carcinogenic process

Lecture 10/22/09

TA: Kristin Yamada

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## Cancer

- Cancer has a large environmental (and genetic) component
  - "Genetics provides the gun, but the environment pulls the trigger"
  - Twin and environmental studies
    - See reader page 128

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## Characteristics of Cancer (1)

- Dependent on regulation of 3 processes:
  - Continued replication
  - Differentiation of cells
  - Apoptosis
- Tissue Cell Number= Cell Proliferation-Cell Death
- Unrepaired DNA mutations can predispose a person to cancer
  - Usually involve genes that function at DNA checkpoints or growth factors
- Usually a long latency between environmental exposure and disease symptoms

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## Characteristics of Cancer (2)

### Stages:

- Initiation: acquire genetic change
- Promotion: clonal expansion of cells
- Progression: more genetic and biological events; enhance the growth advantage; metastasis

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## Characteristics of Cancer (3)

### 3 categories of genes implicated in carcinogenesis:

- Oncogenes: dominant alleles in tumors (proto-oncogenes can mutate into an oncogene)
- Tumor Suppressor Genes: recessive
  - EXAMPLE: p53
- Mutator genes: predispose genome to mutagenic events

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## Carcinogens

- Cause genetic instability
- Direct or Indirect interaction with DNA
  - DNA adducts
  - Intercalation of DNA helix
  - DNA methylations (alters expression)
- Can affect chromosome proteins
- DNA synthesis, DNA repair, or DNA recombination enzymes

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## Skin Cancer Example

- UV light causes pyrimidine dimers (T-T or C-C) in p53 tumor suppressor gene
- If replicated, DNA replication mistakes C as a T due to the dimer. This mutation is now permanent.
- Multiple mutations like this can cause cells to have slow DNA repair or avoid apoptosis

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## Epigenetics- “above the gene”

- The study of heritable changes other than those in the DNA sequence
- Environmental exposures can silence or activate genes (changes in gene expression)
- Addition of functional groups to histone proteins

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## How does this relate to EHS?

- Cancer is a huge public health problem
- Development of cancer is largely due to environmental exposures, and to a lesser extent genetics
  - Preface of reader: “ Environmental contributions to the risk of prostate, lung, breast and ovarian are respectively: 58%, 62%, 67%, and 78%. The bottom line is gene expression is responsible for the progression of the major chronic diseases...”
- As public health professionals, it is important that you have a basic understanding of the carcinogenic process

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GOOD LUCK ON THE  
MIDTERM!!



Midterm is Thursday October 30th  
1:00-3:00 PM  
63-105 CHS  
**\*\*Bring a #2 Pencil for the scantron\*\***

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