"The trouble with learning is that it's always about stuff you don't know."
Nutrition, the Environment, and Cancer
Outline of Presentation

1. What is Cancer?
2. Genetic, Molecular, and Cellular implications of Carcinogenesis
   – Cell signaling: Signals, receptors, signal transduction pathway, transcription factors
   – DNA repair system: Nucleotide Exchange Repair, Base Exchange Repair
   – DNA methylation versus: DNA demethylation: Inactivate versus Activate gene expression
   – Cell cycle and Cell proliferation: Cell cycle regulators, apoptotic pathway, regulating differentiation
3. DNA damage versus DNA mutation
4. Nutrients: lipids, proteins, carbohydrates, nucleic acids
5. High fat, low fiber diet versus Low fat, high fiber diet
6. Reactive Oxygen Species (ROS)
   – Produced from natural cellular processes/reactions
   – Produced from environment (e.g. ionizing radiation)
7. What on Earth are Anti-oxidants?
What is Cancer

- Condition induced by uncontrolled cell proliferation
- Leading to increased and abnormal cell population
- Symptoms are mainly related to the nullification of cellular, tissue, and/or organ functions
- Root cause is genetic abnormality/mutation
  - Hereditary
  - Sporadic
Normal versus Cancerous Cells

- Regulated Cell Cycle and Controlled Cell Proliferation
- Anchorage-dependent Growth and Contact Inhibition
- If necessary, Death by Programmed Cell Death (Apoptosis)

- Uncontrolled Cell Proliferation (Hyperproliferation)
- Mostly, Anchorage-independent Growth and loss of Contact Inhibition
- Death by necrosis
Cell Cycle Checkpoints

1. **G1 Checkpoint**
   (Restriction Point/Start Checkpoint)

2. **G2/M Checkpoint**

3. **M Phase Checkpoint**
   (Metaphase-to-anaphase transition checkpoint)

- **(G0/G1 checkpoint)**
- **(G1/S checkpoint)**
- **(S checkpoint = DNA Replication initiation)**

Is all DNA replicated?

Are all chromosomes attached to the spindle?

Is environment favorable?

METAPHASE-TO-ANAPHASE TRANSITION

ENTER MITOSIS

TRIGGER ANAPHASE AND PROCEED TO CYTOKINESIS

ENTER CELL CYCLE AND PROCEED TO S PHASE

START CHECKPOINT

Figure 17-14 Molecular Biology of the Cell (© Garland Science 2008)
In multicellular organisms, the classic required external signals that act as mitogens are growth factors, cytokines and hormones.

Most cells also exhibit anchorage dependence, in which they must be attached in order to divide.

Most cells also exhibit density-dependent inhibition, in which crowded cells stop dividing.

Many single cells also monitor external nutrient availability and will not divide if it is inadequate.
Four components to ALL signal transduction pathways:

Upstream components:
1. Extracellular signaling molecule = the ligand (ligand biochemistry & mode of delivery)

Downstream components:
2. Receptor
3. Intracellular signal transduction cascade
4. Response
Signal System Cross-Talk
The extent of cross-talk depends on what genes are the expressed within a cell.
Cause

• DNA errors (damages and mutations)
  – DNA replication is major source of errors
  – Free radicals (ROS)

• Mutations in relevant gene(s) can increase chance of carcinogenesis
  – Proto-Oncogenes
  – Tumor Suppressors
  – DNA repair proteins
Disruption or Loss of Existing Genes

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 (i.e., these processes contribute to genetic change much more often than mutation)
When the cell continues to accumulate DNA damages

Can result from bad copies during DNA replication

When the cell continues to accumulate DNA damages

Mdm2 will cause p53 degradation

ATM/ATR kinase activation

Chk1/Chk2 kinase activation

PHOSPHORYLATION OF p53

stable, active p53

ACTIVE p53 BINDS TO REGULATORY REGION OF p21 GENE

p21 gene

stabilized DNA

Figure 17-63 (part 1 of 2) Molecular Biology of the Cell (© Garland Science 2008)
p53 is a critical tumor suppressor gene

Mitotic Cell Cycle & Cell Death

p53 helps multicellular organisms cope safely with DNA damage and other cell stresses by acting as a check on cell proliferation in circumstances where it would be dangerous.

Direct binding of Bcl2 and expression of pro-apoptotic proteins like BH3-only

p21 expression (Permanent cell cycle arrest)
Environmental Effect

Single-stranded and double-stranded breaks can also result from reactive oxygen species (ROS) activity

- ROS are chemically reactive molecules containing oxygen species (eg., oxygen ions and peroxides)

- Generated by either endogenous metabolic processes or exogenous “insults” (cigarette smoke, pollutants, radiation from gamma, UV or X-rays)

- Potential outcomes: gene shuffling, inactivation, altered regulation, or duplication

- DNA repair system that can remove these mutations (to some extent)
Morphological and Genetic Model for Colorectal Adenocarcinogenesis

Inactivation of hMSH2 and hMSL1 (DNA repair genes)

CHROMOSOME:
- 5q
- 12q
- 18q
- 17p

ALTERATION:
- MUTATION or LOSS
- MUTATION
- LOSS
- MUTATION and LOSS

GENE:
- APC
- MCC?
- K-RAS
- DCC?
- p53

Normal Epithelium → Hyperplastic Adenoma (Hyperproliferating Epithelium) → Early Adenoma (Tubular) → Intermediate Adenoma (Tubulovillous) → Late Adenoma (Villous) → Carcinoma → Metastasis

Altered DNA Methylation

Other Genetic Alterations?
Normal, Uninvolved Colon
Hyperplastic Polyps + Adenomatous Polyps
Morphology of Hyperplastic Polyp
Morphology of Hyperplastic Polyp
Pedunculated, Tubular Adenomatous Polyp
Sessile Tubular Adenomatous Polyp
Morphology of Tubular Adenomatous Polyp
Morphology of Tubular Adenomatous Polyp
Villous Adenoma with Focus of Invasive Carcinoma
Morphology of Villous Adenoma with Focus of Invasive Carcinoma
Morphology of Villous Adenoma with Focus of Invasive Carcinoma
Adenocarcinoma
Circumferential Carcinoma (apple-core appearance)
Morphology of Adenocarcinoma
Morphology of Adenoma
Adenocarcinoma with Necrotic Center
Morphology of Necrotic Tissue
Risk Factors

• Hereditary
• Predisposition
• Food intake/diet/nutrition
  – Fat/lipids: saturated, unsaturated, cholesterol, animal versus plant
  – Proteins: red meat, chicken, fish
  – Carbohydrates: simple, complex, processed, fiber
  – Vitamins: water-soluble, water-insoluble
• Environment:
  – Radiation, fine particles, smoking, etc.
• Many more…
Familial Adenomatous Polyposis (100’s)
Familial Adenomatous Polyposis (1000’s)
How food is digested in body?

- Order of digestion of foods/molecules
  - Carbohydrates are digested by saliva components in mouth
Digestive System

• Digestive tract: lips, oral cavity, oral pharynx, esophagus, stomach, small and large intestine, appendix, rectum, and anus

• Digestive glands: Mucous and serous glands, salivary glands, submucous glands, gastric glands.

• Other Organs: liver, pancreas, gall bladder
★ ★ primary organs/ proper

★ ★ secondary organs/ associated

**SALIVARY GLANDS**
- Secretion of lubricating fluid containing enzymes that break down carbohydrates

**PHARYNX**
- Pharyngeal muscles propel materials into the esophagus

**ESOPHAGUS**
- Transport of materials to the stomach

**STOMACH**
- Chemical breakdown of materials via acid and enzymes; mechanical processing through muscular contractions

**PANCREAS**
- Exocrine cells secrete buffers and digestive enzymes; endocrine cells secrete hormones

**SMALL INTESTINE**
- Enzymatic digestion and absorption of water, organic substrates, vitamins, and ions

---

**ORAL CAVITY, TEETH, TONGUE**
- Mechanical processing, moistening, mixing with salivary secretions

**LIVER**
- Secretion of bile (important for lipid digestion), storage of nutrients, many other vital functions

**GALLBLADDER**
- Storage and concentration of bile

**LARGE INTESTINE**
- Dehydration and compaction of undigestible materials in preparation for elimination
Salivary Gland Functions

- Moisten and lubricate food for swallowing
- Secrete enzymes like amylase to begin digestion (of carbohydrates)
- Saliva has protective effect on oral cavity tissues
Functions of G.I. tract Epithelium

• Permeability barrier between gut lumen and blood
• Transport and digest food
• Secretion of enzymes
• Absorb nutrients
• Produce and secrete hormones involved in digestion
Stomach

- Thick muscle layers mix food
- Secretions of enzymes and acid begin digestion
- These enzymes include gastric lipase, rennin, and pepsin (which is secreted as pepsinogen and activated in the lumen)
  - Pepsin hydrolyzes proteins
  - Rennin breaks down milk proteins
  - Lipase initiates the digestion of fats.

Pancreas

- Zymogen granules contain: trypsinogen, chymotrypsinogen, carboxypeptidase, ribonuclease, DNAase, lipase, elastase, amylase

Liver

- Bile contains: water, ions, bile acids, phospholipids, cholesterol, & bilirubin
  - Bile acids solubilize lipids, aid digestion, and metabolize alcohol
How foods increase chance of carcinogenesis?

- High meat/fat consumption correlates with increased incidence of Colorectal Adenocarcinoma
  - Increased bile secreted into stomach
  - Deoxycholic acid and Lithocholic acid
    - secondary bile acids
    - metabolic byproducts of intestinal bacteria
  - Secondary bile acids cause DNA damage
    - increase intracellular production of reactive oxygen and reactive nitrogen species
    - resulting in increased oxidative stress and DNA damage
  - Exercise reduces deoxycholic acid in the colon
How foods increase chance of carcinogenesis?

• High vegetable and fruit consumption

• Two groups of carbohydrates: simple and complex
  – Simple carbohydrates (starch and simple sugars)
    • easily hydrolyzed (broken down) and absorbed in small intestine
  – Complex carbohydrates (cellulose, lignin, pectin = dietary fiber)
    • Resistant to digestion in small intestine
    • Undergo bacterial fermentation in colon instead
    • ability of dietary fiber to reduce the contact time of carcinogens within the intestinal lumen and to promote healthy gut microbiota

• Plants also contain antioxidants (vitamins) and phytochemicals (selenium and calcium)
How foods increase chance of carcinogenesis?

- What happens when microbiota is increased?
  - May lead to inflammation
  - Tissue damage
  - Increased cell proliferation
Treatment using Natural food products

- High fiber, low red meat/fat diet
- Vitamins
  - Antioxidants
    - What are they? Reducing agents
    - How do they work? Donate electrons
    - What are free radicals (ROS)? Extra or missing electrons
    - Are antioxidants effective?
    - Can they do harm? Let’s see
Vitamin E and Vitamin C

• Vitamin E (α-tocopherol):
  – obtained through regular diet or dietary supplements
  – lipophylic, resides within the cell membrane, and acts as an antioxidant

• Vitamin C (Ascorbic Acid)
  – obtained through a regular diet or dietary supplements
  – lipophobic, resides within the cytosol, and acts as an antioxidant
Synergy of Vitamins E & C

• Vitamin E reduces free radicals, causing its own oxidation
• Vitamin C reduces Vitamin E, reactivating Vitamin E
• NADH present within the cell reduces Vitamin C, reactivating Vitamin C
• Once both vitamins have been reduced, each is available to reenter the cycle