609G: Concepts of Cancer Genetics and Treatments (3 credits)


Course Description: Concepts of Cancer Genetics and Treatments is designed to provide knowledge of common genetic causes of cancer and how they relate to current treatments. The course will discuss heritable gene predisposition, somatic mutational causes and how the environment contributes to the disease. Students will learn about common genes and pathways associated with cancers and how current treatments target and utilize the commonalities of cancers.

Proposed Syllabus

Module 1 – Mutations and Cancer – Page 5-25, 30, 40-48, 125-139

1) Genetic Mutations
   a. Standard mutation rates
   b. Splicing errors
   c. Rearrangement/translocation
   d. Radiation – UV, other
   e. Carcinogens

2) Epigenetic changes
   a. HDAC, HATs
   b. Telomere extension
   c. Senescence

3) Genetic Instability
   a. Aneuploidy
   b. Mismatch repair
   c. DNA repair defects

4) Somatic versus Germline mutations

Module 2 – Common Cancers and their causes – Chapter 6

1) No two cancers are the same
   a. Persons unique genetic makeup contributes to the disease

2) Many common genes are mutated in different cancers
   a. Some genes like P53 are mutated in many different types of cancers
   b. Some pathways like the RAS pathway are commonly affected in different types of cancers
3) Most cancers arise from a specific cell type
   a. Epithelial cells are the origin of most solid tumors
   b. Leukemias
   c. Brain tumors rarely from neurons
   d. Why?

4) Understanding the disease language
   a. Incidence
   b. Mortality
   c. Prevalence

Module 3 - The Oncogene and Tumor Suppressor – Chapters 2 and 3

1) Oncogenes promote cell survival and replication
   a. Src, ERK, RAS, HER2
   b. Activation by mutation
   c. Activation by overexpression
   d. Activation by amplification
   e. Activation by translocation – Bcr-Abl

2) Tumor Suppressor genes turned off
   a. Apoptotic pathway - Bcl
   b. Cell Cycle regulators – P53
   c. DNA Repair – BRCA
   d. Two hit hypothesis

Module 4 – Change in Function of gene product

1) Gain of Function
   a. Most oncogenes are GOF
   b. Single point mutation can lead to activation
   c. Deletion of regulatory c-terminal domain
   d. Splicing error deletion of regulatory domain
   e. Splicing error creates “new” gene product
   f. Mostly somatic mutations

2) Loss of Function
   a. Most tumor suppressors LOF mutations lead to cancer
   b. Require “two – hit”
   c. Often Germline mutations
   d. Can be single point mutation in active site
   e. Deletion – PTEN
   f. Splicing errors

3) Dominant Negative
   a. Mostly mutation that renders catalytic activity of a protein disabled, but can still bind normal partners. Maybe increase binding.
   b. Loss of function mutation that does not require two-hit
   c. Mutated gene product blocks wild type from doing its normal function
   d. Mostly tumor suppressor and key pathway regulators
Module 5 – Cellular effects – Chapter 4

1) Cumulative effects
   a. Lack of DNA repair leads to further mutations
   b. Failure to apoptosis leads to Polyploidy
   c. Cancer may have an origin cell, but is a diverse disease – leads to recurrences

2) Oncogene Addiction
   a. As certain pathways take over (GF pathway), others neglected and selected against
      i. Increased mutation and faster replication leads to greater selection
      ii. Cancer becomes “Addicted” to a certain pathway
   b. Makes for targeted therapy
   c. Examples – HER2 in Breast Cancer, ER in BC, AR in Prostate Cancers, Src in Sarcomas, BCR-ABL in CML

3) Rapidly reproducing cell with little DNA repair and no check points
   a. Cell can replicate to an non-sustainable point
   b. Can be targeted with agents that increase DNA damage

Module 6 – Cancer Gene Pathways – Chapter 5

1) Pathways defined by biochemical reactions
   a. Protein-Protein Interactions
   b. Multistep pathways
   c. Chemical modifications

2) Phosphorylation cascades
   a. Tyrosine Kinases
   b. Receptor Tyrosine Kinases
   c. Membrane associated phosphorylation
   d. GTPases

3) Common pathways associated with Cancer
   a. RAS
   b. PI3K/AKT
   c. EGFR
   d. TNF family receptors

4) Gate keeper pathway
   a. MDM/P53

Module 7 – Standard Therapies – Pg 268-269 and supplemental materials

1) Chemotherapy
   a. Chemical agents that damage DNA
   b. Cause double stranded DNA breaks in excess
   c. Hope healthy cells arrest at cell cycle check points
   d. Hope cancer cells have unsustainable DNA damage and “die”
e. Kills most rapidly reproducing cells – Muscousal linings (mouth, guy, intestines, etc.), hair follicles, bone marrow, etc.
f. Tricky dosing to find the sweet spot

2) Radiation
a. Radioactive rays used to damage DNA
b. Same basic principle of chemotherapy
c. Can be more targeted
   i. Directed rays
   ii. Radioactive beads
d. Risk of “new” cancer as a result

Module 8 – Targeted Therapies – Page 269-277 and supplemental materials

1) Monoclonal antibodies
a. Target cell surface membrane proteins - RTK
b. Almost always oncogenes – HER2
c. Block GF binding and limit activity – dominant negative activity
d. Dimerize and trigger downregulation of protein
e. Limitations
   i. Delivery and targeting – Systemic delivery and thus indiscriminate binding
   ii. Cancer has to be sensitive to blocking of RTK.
   iii. Non-permeable
   iv. Cleared by the body
   v. Not chemical synthesized – production limitations
f. Advantages
   i. In and of themselves, low toxicity
   ii. Targeted to certain cells so increase specificity
   iii. Side effects often much less severe than chemotherapy

2) Small Molecule Inhibitors
a. Small molecules that inhibit oncogenes
b. Mostly targeted to active sites of enzymes
c. Mostly commonly block ATP binding in kinases
d. Limitations
   i. Off target effects
      1. Active sites of many enzymes are similar and conserved
      2. Hard to target JUST the oncogene
      3. Blocks signaling in healthy cells too
   ii. Delivery
      1. Must be soluble for systemic delivery
      2. Chemical properties of solubility often decrease efficacy of the drug
      3. Cell membrane permeability leads to indiscriminate cell type targeting
   iii. Short half life in bodies
      1. Easily excreted from cells
2. Quickly removed from body
   e. Advantages
      i. Much more specific than chemotherapy and radiation
      ii. Soluble and permeable – increase delivery to cells over mAb.
      iii. Production of drug can be easily scaled to demand – Chemically synthesized
      iv. Cheaper generics once off patents

3) Combination therapies
   a. Adjuvant
      i. Chemo and targeted radiation
      ii. Chemo and small molecule inhibitor
   b. Immunotoxin
      i. mAb with chemotherapeutic agent attached.
      ii. Targeted chemotherapy

Module Terms, Concepts and Discussions
Module 1

Key Terms
Mutation
   Sense
   Missense
   Nonsense
   Deletion
   Translocation
Miss-match repair
Single strand DNA break
Double strand DNA break
Epigenetics
Histones
Acetylation
Methylation
Phosphorylation
Ubiquitylation
“Histone Code”
Telomere
Telomerase
Senescence
Apoptosis
Autophagy
Cell Cycle
Growth Factors
Ploidy
Aneuploidy
Somatic Mutation
Germline Mutation
Clonal disease

Key Concepts
1. Cancer is a complex disease
2. Four factors contribute to the disease (Genetics, behavior, environment, luck)
3. Mutations are a natural part cell division
4. More than just sequence contributes to cancer genetics
5. Germline genetic sequence can predispose people to develop cancer when somatic mutations are introduced

Discussion #1

Describe and define how the four contributing factors can lead to cancer. Be sure to explain the role of each factor and how it relates to the others. Use specific examples of all four factors to strengthen your position.

Module 2

Key Terms
Tumor heterogeneity
Incidence
Mortality
Prevalence
Epithelial
Endothelial
Carcinoma
Adenoma

Key Concepts
1. Many cancers are caused by the same genetic mutations, yet those same genetic mutations do not lead to cancer in all tissues or persons.
2. The environment of a tissue makes cells more or less sensitive to certain mutations.
3. Cancer rates are described in three main terms, Incidence, Mortality and Prevalence.
4. A persons genetic makeup, environment and behaviors affect prevalence and mortality.
5. No two cancers are the same.
6. Most solid tumors derive from epithelial cells.

Discussion #2

Pick three common cancers and compare and contrast the causative events. Be sure to develop an explanation why a mutation in one organ or tissue would be more likely to lead to cancer than another. Explain why a mutation in one gene would more likely lead to cancer in one tissue and not another. Also explain why the prevalence and mortality rates differ based on various factors such as location (environment), and ethnic and genetic background.
Module 3

Key Terms
Oncogene
Tumor Suppressor Gene
Activation
Overexpression
Amplification
Translocation
Gate Keeper
G1 Checkpoint
G2 Checkpoint
Two-Hit Hypothesis

Key Concepts
1. There are two “types” or families of genes that cancer favors: Oncogenes and Tumor Suppressor genes
2. Oncogenes are genes that when activated, overexpressed or amplified promote cell survival and replication
3. Tumor Suppressor genes are genes that when deactivated, downregulated or deleted lead to disregulated cell cycles, poor DNA repair and non-functioning apoptosis.
4. Oncogenes can be activated by a mutation that leads to constitutive active, mutations that lead to overexpression of the gene product and genetic amplification that leads to elevated gene products
5. Some oncogenes are “created” by translocations that combine the certain domains of different genes to create a new gene.
6. Tumor Suppressor genes are deactivated by genetic mutations that inactivate the protein or prevent it binding a necessary partner. They can also have their expression lowered by a mutation or be deleted.

Discussion #3

Defend or debunk both of the following statements:

“Amplification of an oncogene will have the oncogenic potential as overexpression of that same oncogene.”

“The two-hit hypothesis for tumor suppressor gene caused cancer requires that the same gene be mutated in the same cell at separate times.”

Use specific examples and consider this a court of law where the burden of proof is beyond a reasonable doubt.
Module 4

Key terms
Gain of function
Loss of function
Dominant Negative
Regulatory domain
Active domain
Gene product
Protein-protein interaction

Key Concepts
1. Changes to genes themselves have little effect on cellular functions unless it affects the gene product (mostly commonly proteins).
2. Gain of function mutations can affect a single allele and have catastrophic event.
3. Loss of function mutations most often need to affect both alleles for altering cellular fates and functions.
4. Dominant negative mutations lead to a gene product that has lost its function. However, they are still able to interact with their normal binding partners and can thus block functional enzymes from their normal function.

Discussion #4

Present an example of a gain of function, loss of function and dominant negative mutation that is known to contribute to oncogenesis. Describe the genetic mutation, the effect on the gene product and the mechanism of action of each in oncogenesis.