Neoplasia IV: Cancer Pathogenesis
Cancer Pathogenesis Lecture Objectives

• Briefly answer, in your own words, the question “What causes cancer?”

• List the eight characteristics (or hallmarks) of cancer cells that make them different from normal cells.

• Explain what proto-oncogenes and oncogenes are.

• Describe what the RAS protein normally does, and explain how it causes cancer when it is mutated.

• Describe what tumor suppressor genes are.

• Describe what the RB protein normally does, and explain how it causes cancer when it is mutated.

• Describe the normal functions of p53, and explain why it’s mutated in most tumors.
Cancer Pathogenesis Lecture Objectives

• Describe the normal function of telomeres, and explain how tumor cells exploit this function.
• Describe the basic steps involved in invasion and metastasis.
• Explain what the Warburg effect is, and explain why tumor cells opt to use it.
• List some ways tumor cells can evade immune detection.
What causes cancer?

Non-lethal genetic damage.
Hallmarks of Cancer

- Evasion of immune detection
- Autonomous cell proliferation
- Resistance to growth-suppressing signals
- Evasion of apoptosis
- Altered metabolism
- Ability to invade and metastasize
- Angiogenesis
- Immortality
Hallmarks of Cancer

Autonomous cell proliferation
Autonomous Cell Growth

- Proto-oncogene: a normal gene whose product promotes cell growth.
- Oncogene: a mutated proto-oncogene. Causes tumor cell to grow autonomously.
- Oncoprotein: the product of an oncogene.
The RAS Gene

- RAS is a signal transduction protein
- Mutated RAS is always on...
- ...therefore, always transducing signals...
- ...therefore, cell is always dividing.
Hallmarks of Cancer

- Autonomous cell proliferation
- Resistance to growth-suppressing signals
Resistance to Growth-Suppressing Signals

- Tumor suppressor gene: a normal gene whose product suppresses the cell cycle (like brakes on a car).
- Mutate these guys, and you lose the brakes!
- Must mutate both copies of the gene to cause tumors.
The Retinoblastoma (RB) Gene

• RB gene product stops cell at $G_1$ checkpoint
• Mutant RB is inactive; lets cells pass through $G_1$!
• Patients with two mutated RB genes have very high risk of retinoblastoma (and an increased risk of getting other tumors).
The Cell Cycle

- Chromosome duplication
- Check for DNA damage (G1/S checkpoint)
- Restriction point
- Centrosome duplication
- Growth in mass
- G1
- S
- G2
- Check for damaged or unduplicated DNA (G2/M checkpoint)
- Mitosis
- M
- Cell division
- G0
Hallmarks of Cancer

- Autonomous cell proliferation
- Resistance to growth-suppressing signals
- Evasion of apoptosis
Evasion of Apoptosis

• Many proteins are involved in apoptosis:
  • p53
  • Fas (the “death receptor”)
  • Executioner caspases
  • BCL2 protein family
• If genes for these proteins are mutated, the cell will be able to avoid killing itself.
The p53 Gene

- Nickname for p53: “guardian of the genome”
- If a cell’s DNA is damaged, p53 causes a pause in the cell cycle (via RB), so DNA can be repaired.
- If DNA damage is irreparable, p53 causes the cell to undergo apoptosis.
- Most human tumors have p53 mutations!
Ionizing radiation, Carcinogens, and Mutagens stimulate DNA damage. When p53 is normal and activated, it leads to cell cycle arrest. If p53 is not activated, there is no cell cycle arrest or DNA repair, leading to the formation of a malignant tumor. If p53 is activated, DNA repair can occur, and successful repair results in normal cells, while repair failure leads to apoptosis.
Hallmarks of Cancer

- Autonomous cell proliferation
- Resistance to growth-suppressing signals
- Evasion of apoptosis
- Immortality
Immortality

• Normal cells can only undergo 60-70 doublings
• Main reason: telomere shortening!
• Stem cells and cancer cells use telomerase to maintain telomere length and keep replicating.
Telomeres

As cells divide over time...
Binding of telomerase

Extension of 3' end

DNA polymerase completes lagging strand
A simple plan for *measurably younger cells* that may help you live a longer, healthier life.

WE GIVE YOU EVERYTHING YOU NEED TO SUCCEED

A monthly smart-supplement regimen, plus before & after DNA tests to measure the improvement in your cells’ biological age based on changes in their telomere length.

1. **Baseline DNA Test**
2. **Take Daily**
3. **Real Results:**
Your expected telomere length: 0.96

Your measured telomere length: 1.12

Your Results

Your Average Telomere Length is 1.12 (T/S ratio) which puts you in the 85th percentile. This means that your telomeres are longer than 85% of women your age.
Your actual age: 52 years

The age of your cells: 36 TeloYears, Younger than your Actual age

Your Results

Your Average Telomere Length is 1.12 (T/S ratio) which puts you in the 85th percentile. This means that your telomeres are longer than 85% of women your age.
Hallmarks of Cancer

- Autonomous cell proliferation
- Resistance to growth-suppressing signals
- Evasion of apoptosis
- Immortality
- Angiogenesis
Angiogenesis

- Tumor cells need blood too!
- Can’t grow >1-2 cm without new vessels
- Tumor cells eventually learn how to stimulate angiogenesis
- Lots of cytokines involved (i.e., VEGF)
Tumor cells surrounding new vessel
Hallmarks of Cancer

- Autonomous cell proliferation
- Resistance to growth-suppressing signals
- Evasion of apoptosis
- Immortality
- Ability to invade and metastasize
- Angiogenesis

[Diagram showing the hallmarks of cancer with a central cell surrounded by arrows indicating each hallmark]
Ability to Invade and Metastasize

To do this, tumor cells must:
• Loosen contacts between cells
• Degrade extracellular matrix
• Migrate away from the original site

Some tumors lodge in nearest capillary bed; other tumors show tropism.
Tumor cells surrounding and invading vessel
Hallmarks of Cancer

- Autonomous cell proliferation
- Resistance to growth-suppressing signals
- Evasion of apoptosis
- Immortality
- Ability to invade and metastasize
- Altered metabolism
- Angiogenesis
Altered Metabolism

- Normal cells, when oxygen is around, use oxidative phosphorylation to generate ATP.
- Cancer cells are different!
- They take up *tons* of glucose, and convert it to lactate via the glycolytic pathway.
- This is called aerobic glycolysis, or the “Warburg effect.”
**Normal cells**

- $O_2$ present
- Glucose → Pyruvate → Oxidative phosphorylation → 36 ATP per glucose
- $O_2$ absent
- Glucose → Pyruvate → Anaerobic respiration → 2 ATP per glucose

**Rapidly dividing cells**

- $O_2$ present or absent
- Glucose → Pyruvate → Anaerobic respiration → 2 ATP per glucose

**Tumor cells**

- $O_2$ present or absent
- Glucose → Pyruvate → Anaerobic respiration → 2 ATP per glucose
Normal cells

- Oxygen present: Oxidative phosphorylation
- ATP: 36 per glucose

Rapidly dividing cells

- Oxygen absent: Anaerobic respiration
- ATP: 2 per glucose

Tumor cells

- Oxygen present or absent: Anaerobic respiration
- ATP: 2 per glucose

Genes:
- DNA
- RNA
- Structural proteins
- Lipids
- Organelles
Hallmarks of Cancer

- Autonomous cell proliferation
- Resistance to growth-suppressing signals
- Evasion of apoptosis
- Immortality
- Ability to invade and metastasize
- Altered metabolism
- Evasion of immune detection
- Angiogenesis
**Antitumor Immunity**

- **Failure to produce tumor antigen**
  - Antigen-loss variant of tumor cell
  - Lack of T cell recognition of tumor

- **Mutations in MHC genes or genes needed for antigen processing**
  - Class I MHC-deficient tumor cell
  - Lack of T cell recognition of tumor

- **Production of immunosuppressive proteins or expression of inhibitory cell surface proteins**
  - Inhibitory ligand
  - Inhibitory receptor
  - Immunosuppressive cytokines
  - Inhibition of T cell activation