If It’s Broke, Fix It
DNA Damage, Mutation, and Repair

Ben Morris
Outline

• What is cancer and how is DNA involved?
• How does DNA repair work and how do defects cause cancer?
• How does this understanding help us treat cancer?
Outline

• How does DNA repair work and how do defects cause cancer?
  – What is a mutation?
  – How does DNA get mutated?
  – How do cells fix damaged DNA?
  – How does DNA damage contribute to cancer?
The Central Dogma

Instructions for making each protein are encoded in DNA as a gene; THE CENTRAL DOGMA of biology

FUNCTION (Control Growth)
The Central Dogma

DNA (instructions)

ATTGCAACATTGTAGT

gene

protein

Protein (tools)

Janekpfeifer 2006
What is a Mutation?

ATTGCAACATTGTAAGT
What is a Mutation?

ATTGCAACATTGTAGT
What is a Mutation?

A mutation is a permanent change in the DNA sequence of a gene.
Types of Mutations

To be or not to be that is the question

- Point mutation
  - To be or not to we that is the question
- Frame shift
  - To be the question
- Deletion
  - To be the question
- Fusion
  - To be or not to be you and me could write a bad romance
Broken Genes

ABNORMAL FUNCTION
Uncontrolled Growth
Ex: Chronic Myelogenous Leukemia

CML situation

- ABL Kinase
- Growth Accelerators
- Mutated Kinase (BCR-ABL)
- Activity "flag"

It’s like a lead foot on the gas pedal.
Questions?
How does DNA get mutated?
Environmental

Inherited

Age related
The Structure of DNA

Backbone

Bases

ATTGCAACATTTGTAAGT
ACTACATGTTCGAT
Types of Mutations

- Environmental
- Inherited
- Age related
Environmental Mutagens

It all starts with DNA damage

X-Rays: Double-strand breaks

UV-B: crosslinks adjacent bases

Smoking: chemical adducts
Environmental Mutagens

- Mutations happen when cells try to fix DNA damage
- Damage is not the same as a mutation!
Inherited Mutations

• Familial Cancer Predisposition
• BRCA1/2, Fanconi Anemia, Xeroderma Pigmentosum
Age Related Mutation

• Cells make mistakes copying DNA
• Cell metabolism can damage DNA
• The longer your cells are alive (and the more of them you have) the more likely they will be mutated
Questions?
Mutation is Not Always Bad

• Most mutations don’t really matter
  • i.e. To be or not to we that is the question
• Some mutation is good
  • Evolution!
• Cells have safety nets to protect against harmful mutations
  • DNA damage repair
  • Self-destruct
• Cancer needs more than one mutation
Mutations and Cancer

• Growth regulation (gas and break)
  → Cells grow faster and don’t stop

• Self-destruct
  → Cells don’t die when they start going bad

• DNA damage repair
  → Cells accumulate other mutations faster
DNA damage repair

- Lots and lots of repair machines for specific kinds of damage
- Repair machines are frequently mutated in cancer

BRCA1/2

Xeroderma Pigmentosum
Fanconi Anemia

- Cancer predisposition syndrome
- A family of genes are mutated in patients
- Cells are sensitive to inter-strand crosslinking chemicals
- Type of damage?
- Cause of damage?
- What do the genes do?
But wait!
Summary

• Cancer is a genetic disorder
• Mutations drive cancer development
• Mutations can be inherited or accumulated during a person’s life
• Mutations of DNA damage repair genes accelerate cancer development