Genetics of Cancer

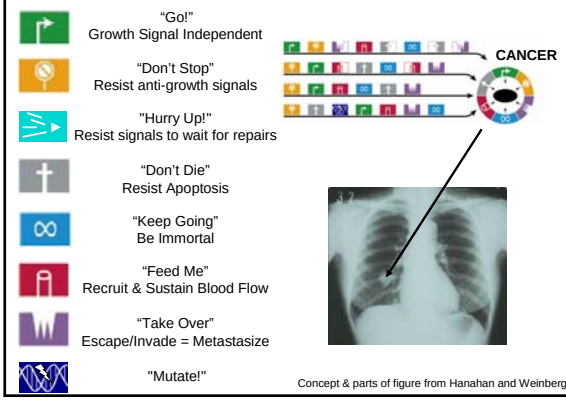
Lecture 35

"Cancer III"

Prof. Bevin Engelward, MIT Biological Engineering Department

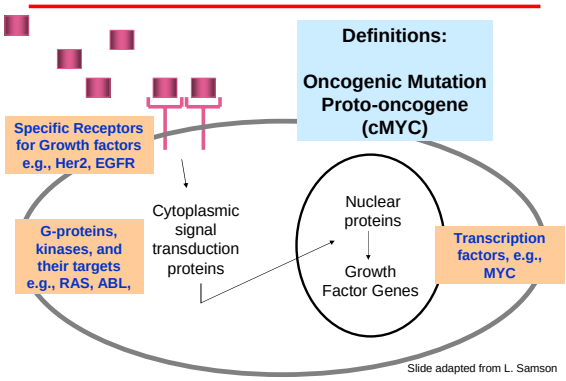
Based on a lecture by Prof. Leona Samson

Normal Cell → Metastatic Cancer: Many Changes Necessary



Concept & parts of figure from Hanahan and Weinberg

Signal Transduction and Growth Regulation



Slide adapted from L. Samson

Take-Home Messages

- RTK→RAS→RAF→MEK→MAPK→TF→"Go!"
- Cancer is a disease of over-prolif; it's advantageous to cancer cells to trick cells into "Go!"
- Cancer cells need many new traits, therefore multiple mutations (proliferation is one such trait)
- Many cancers experience a high mutation rate, so its hard to know which mutations matter to cancer
- Most carcinogenic mutations occur in somatic cells, but they can also arise in germline or during development

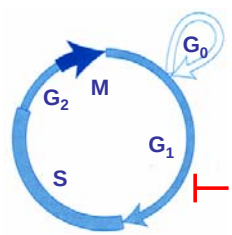
Mutations in Cancer Genes Transform Normal Cells into Cancer Cells

Oncogenes
gene that makes a cell cancerous
dominant gain-of-function mutations

Tumor suppressor genes
genes that normally restrain growth
recessive, loss-of-function mutations

Example of a Tumor Suppressor Gene:

RB - Normally this protein inhibits proliferation
Loss of RB promotes cell division



Definitions:

Retinoblastoma (RB)
Restriction Point

RB controls the Restriction Point

Slide from L. Samson

RB – the Retinoblastoma Gene – was the first example of a Tumor Suppressor Gene

Loss of function of RB leads to malignant tumors of the retina during the first few years of life

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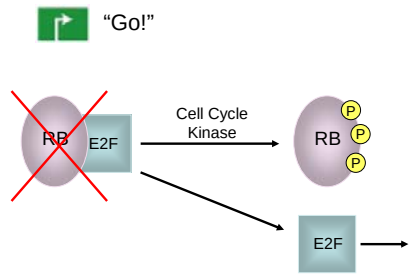
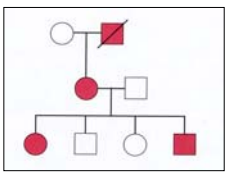
Phosphorylation of RB at the appropriate time in G1 allows release of the E2F Transcription Factor



The Retinoblastoma disease behaves as an autosomal **dominant** trait



- In order to lose cell cycle control MUST lose function of both alleles
- But, for Mendelian inheritance of RB, children need only inherit only one non-functional allele
- To explain this, the "TWO HIT" hypothesis was proposed
- During development of the retina a second mutation is almost certain to occur
- RB is one of the very few cancers that seems to require defects in only one gene (but in both alleles)

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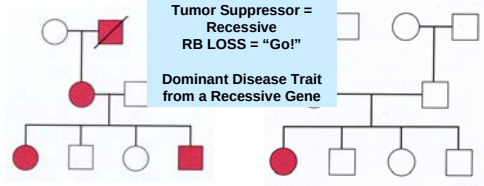
Two ways to get retinal tumors due to loss of RB function

Mendelian **Sporadic**

Definitions:

Tumor Suppressor = Recessive
RB LOSS = "Go!"

Dominant Disease Trait from a Recessive Gene



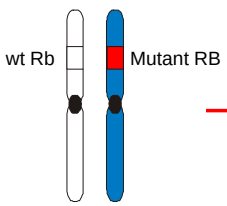
Germline Mutation + Somatic Mutation

Bilateral
Early Onset

Somatic Mutation + Somatic Mutation

Single Tumor
Unilateral
Later Onset

How is the second RB allele rendered non-functional?



Heterozygous for RB mutation

Loss of Heterozygosity

LOH

This can happen is several ways

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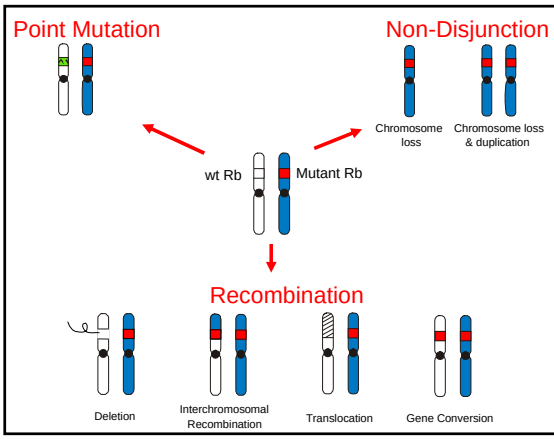
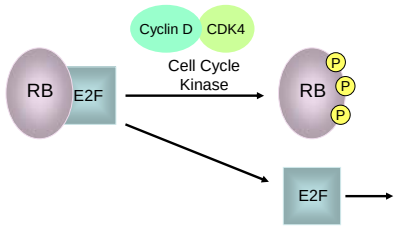


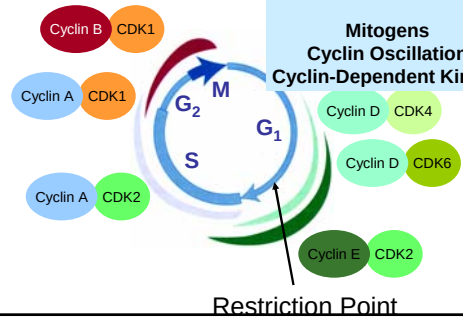
Cyclin-CDKs Regulate RB



Autonomous "Cell Cycle Clock": Cyclins & CDKs

Definitions:

Mitogens
Cyclin Oscillation
Cyclin-Dependent Kinase

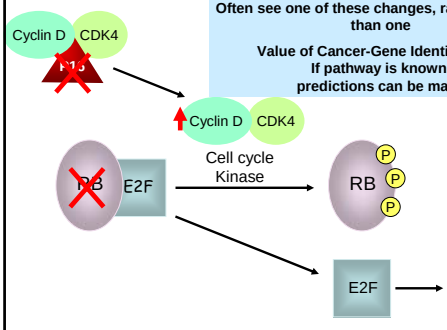


RB is part of a Pathway: Several Vulnerable Steps

Important Points:

Often see one of these changes, rarely see more than one

Value of Cancer-Gene Identification: If pathway is known, predictions can be made



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gene that makes a cell cancerous
dominant gain-of-function mutations

Example of a Mutator Gene:

UvrA - Normally helps repair DNA damage
LOSS of UvrA ↑ Odds of Sunlight-Induced Mutation

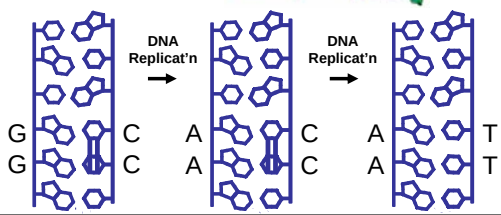
Mutator genes
↑ spont. & environmentally induced mutation rates
usually recessive, loss-of-function mutations

Sunlight Damages DNA

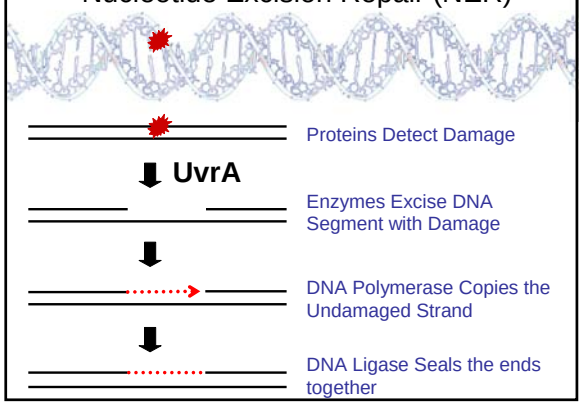
Definitions:

Pyrimidine Dimer
Signature Mutation
Damage vs Mutation

CC to TT



Nucleotide Excision Repair (NER)



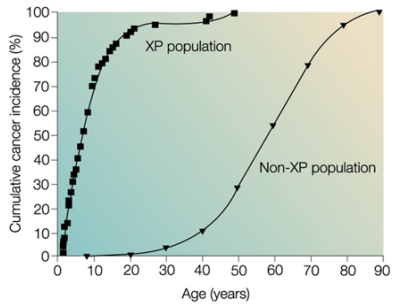
Xeroderma Pigmentosum (NER deficiency)

Inheritance of <u>two</u> mutant copies of UvrA can cause XP

Autosomal Recessive Disease

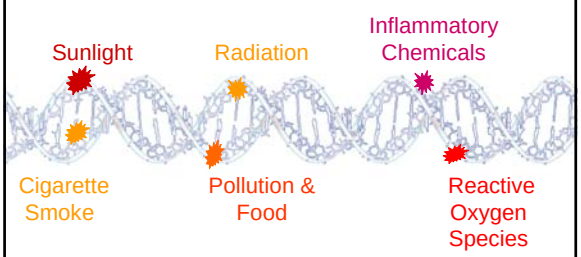
2000-fold increased risk of skin cancer

Age at First Skin Cancer

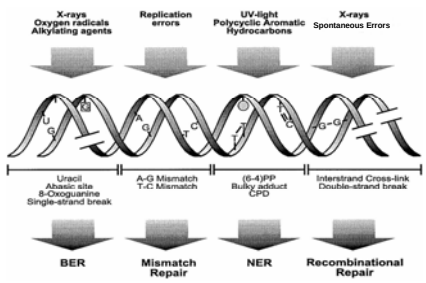


NER Pathway - Normally helps repair DNA damage
Mutator phenotype accelerates cancer onset

UV is one of Many Types of DNA Damage

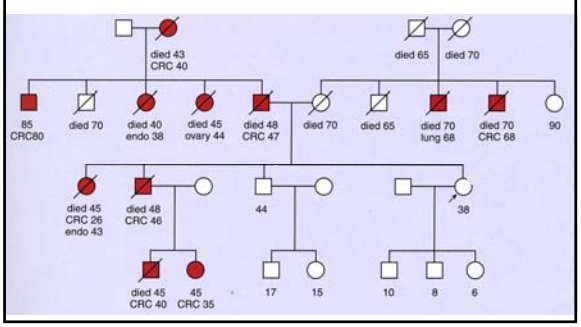


Many Other Cancer Prone Syndromes are caused by Deficiencies in DNA Repair

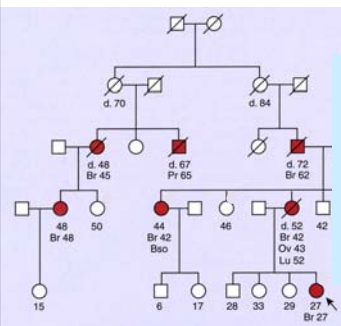


If DNA Repair pathway is defective →	Colon	Colon Ovary Endometrial	Skin	Breast Ovary Leukemias

Hereditary Nonpolyposis Colon Cancer
DNA Mismatch Repair Defect
Syndrome inherited as Autosomal Dominant



Hereditary Breast Cancer Susceptibility
DNA Recombination Repair Defect
Syndrome inherited as Autosomal Dominant



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Tumor suppressor genes
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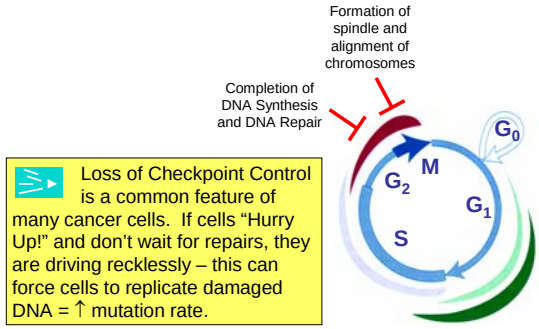
Checkpoint Genes are Tumor Suppressors:

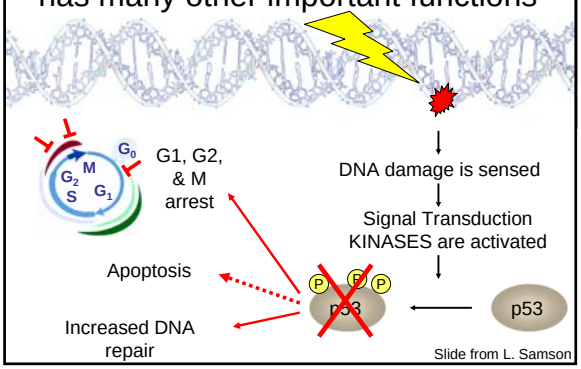
p53 - Signals cells to "WAIT!" if there is DNA Damage
Loss of normal p53 function increases mutation rate

Checkpoint Control Pathways provide Negative Feedback on the Cell Cycle



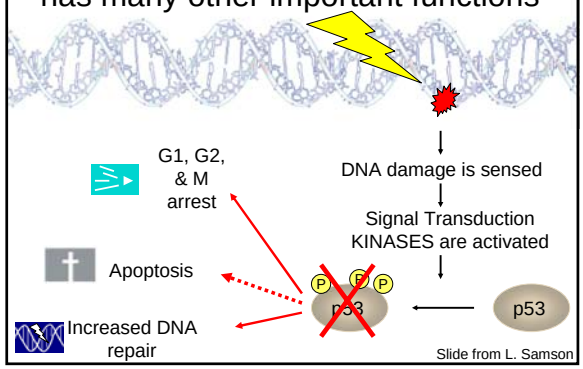
Loss of Checkpoint Control is a common feature of many cancer cells. If cells "Hurry Up!" and don't wait for repairs, they are driving recklessly – this can force cells to replicate damaged DNA = ↑ mutation rate.

P53 Helps Cells to Stop for Repairs & has many other important functions



Slide from L. Samson

P53 Helps Cells to Stop for Repairs & has many other important functions



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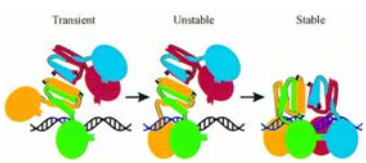
P53 is a Tetrameric Transcription Factor

Definitions:

Checkpoint Mutant
Multifaceted Tumor Suppressor
Dominant Negative

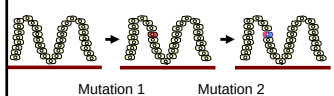


McLure & Lee

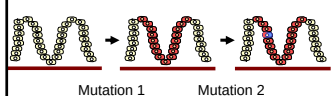
DOMINANT NEGATIVE mutations are common

Most fully blown cancers require many mutations

How do you get two mutations into the same cell?

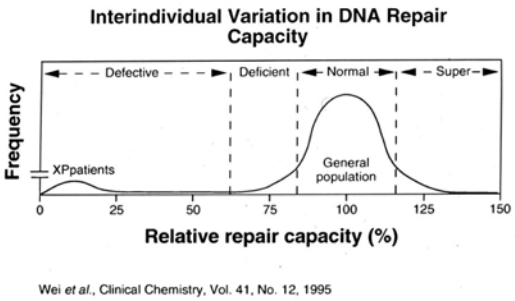


Increase the Mutation Rate



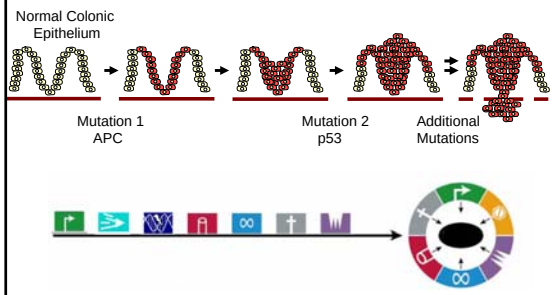
Clonally Expand Mutant Cells

Xeroderma Pigmentosum ~ 1/250,000



Wei *et al.*, Clinical Chemistry, Vol. 41, No. 12, 1995

One thing leads to another…



http://music.msn.com/album/?album=29452880#

So, where do mutations come from?!

- UV, Aflatoxin and other environmental carcinogens (signature mutations)
- Spontaneous errors in DNA metabolism, e.g., immunoglobulin machinery gone awry, polymerase errors
- Spontaneous DNA breakdown and damage
- Problems in DNA metabolism and repair

Take-Home Messages

- Tumor suppressors are recessive genes; inheritance of one broken copy can lead to a dominant trait
- Mutator Genes are a class of tumor suppressors that, if lost, lead to a mutator phenotype
- There are many more ways to inactivate a gene than to create an oncogenic mutation; thus it is difficult to screen the population for carriers
- Four ways to increase the odds of a cancer-promoting mutation: decrease DNA repair, increase DNA damage, disrupt checkpoints, clonally expand – these are all cancer traits

Where do cancer cells come from?

"Survival of the Fittest"
is Happening in You Right Now

What can you do to decrease your odds of cancer?

REDUCE THE NUMBER OF CELL DIVISIONS YOU EXPERIENCE

REDUCE MUTAGENIC EXPOSURES