Genetics of Cancer

Lecture 35

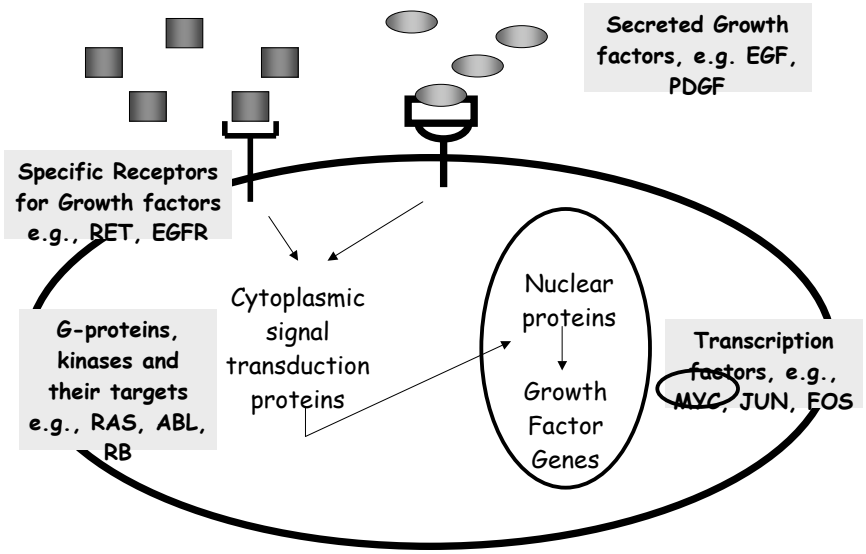
Alterations in different kinds of Genes cause Cancer

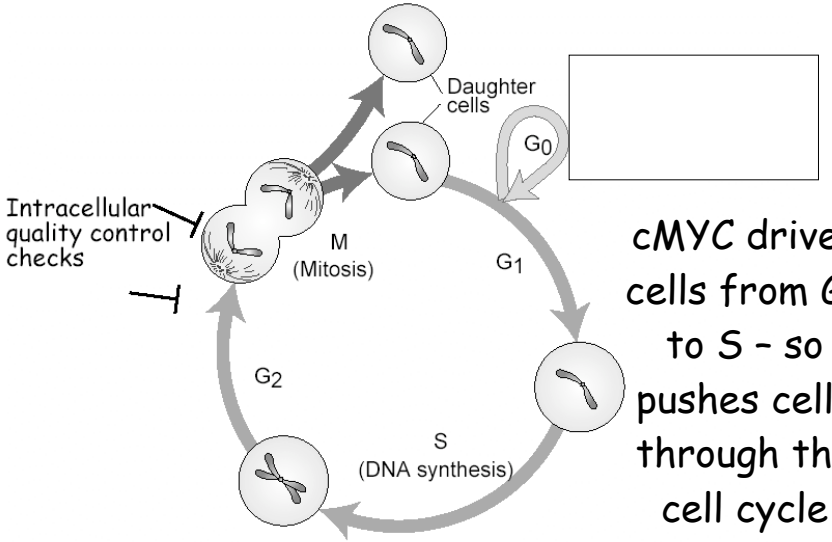
Oncogenes
dominant gain-of-function mutations
promote cell transformation

Tumor suppressor genes
recessive, loss-of-function mutations
promote cell transformation

Mutator genes
Usually recessive, loss-of-function mutations
that increase spontaneous and environmentally

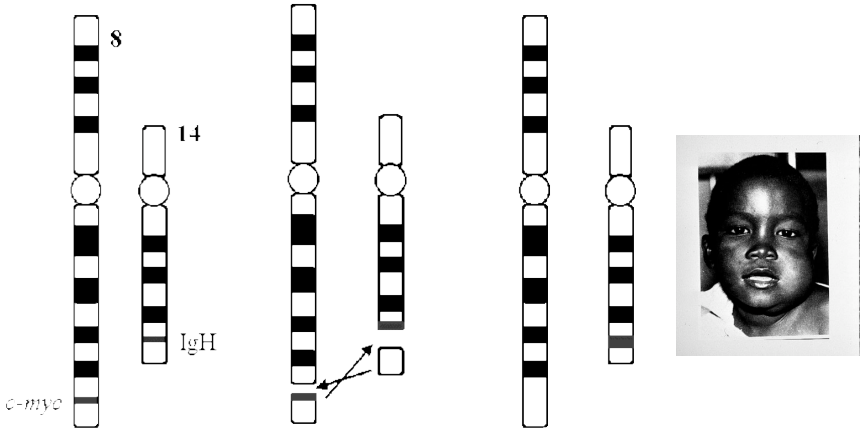
Signal Transduction and Growth Regulation





cMYC drives cells from G1 to S – so pushes cells through the cell cycle

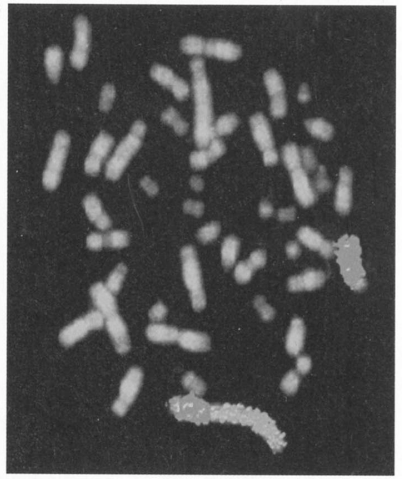
Burkitt's Lymphoma: A chromosome translocation
→ cMYC to be expressed inappropriately in B-cells



cMYC drives cells from G1 to S

Another way that oncogenic transcription factors can be up-regulated: Gene Amplification

Chromosome from a TUMOR



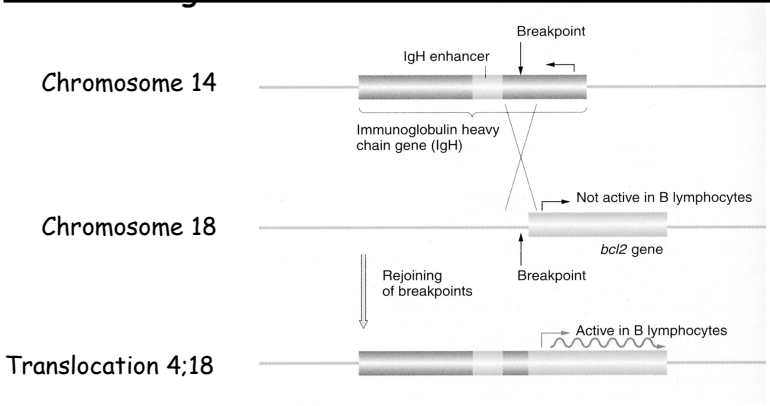
Blue – staining of all chromosomes

Red – staining of chromosome 4

Green – staining of the N-MYC gene

(N-MYC and cMYC share

One more example – with an interesting twist
A translocation between Chr 14 and Chr 18 to put the BCL2 gene under the strong IgH promoter



The BCL2 protein PREVENTS programmed cell death, B cells live longer than normal leading to B-cell Lymphomas

What chromosomal events convert proto-oncogenes to dominantly acting oncogenes

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- Chromosomal translocation to juxtapose a strong promoter upstream and the proto-oncogene such that it is inappropriately expressed (e.g., cMyc, Bcl2)
- Gene amplification resulting in overexpression

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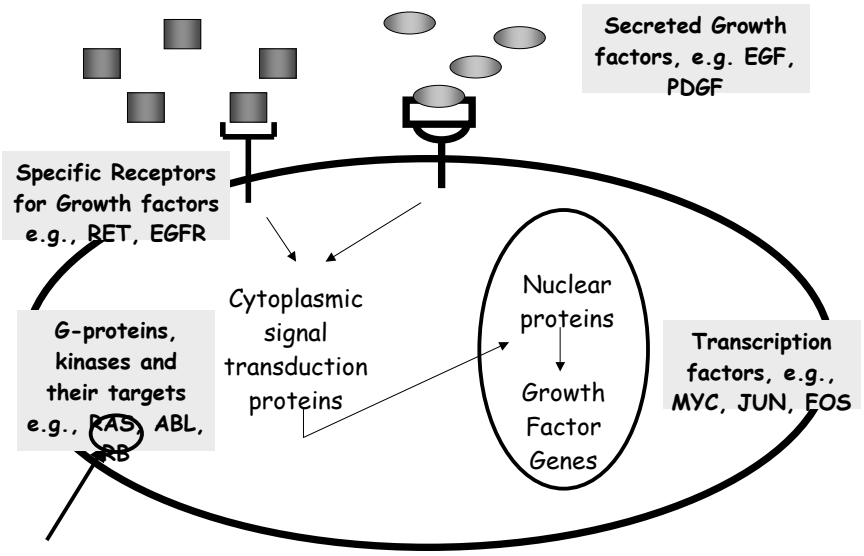
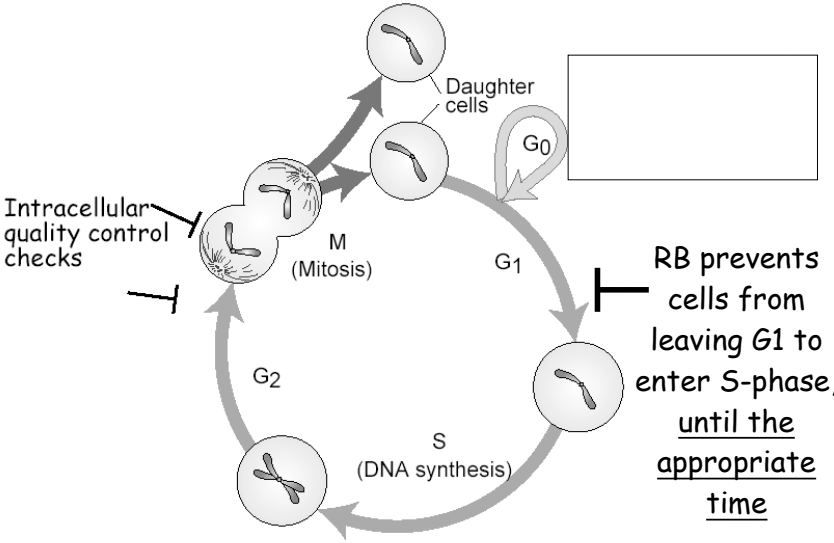
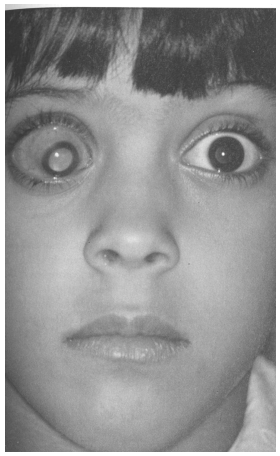
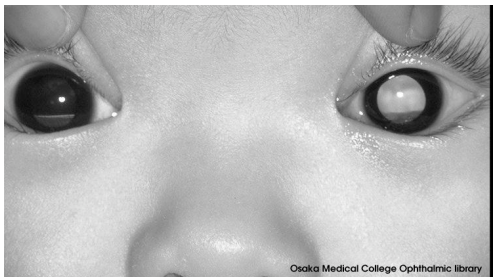




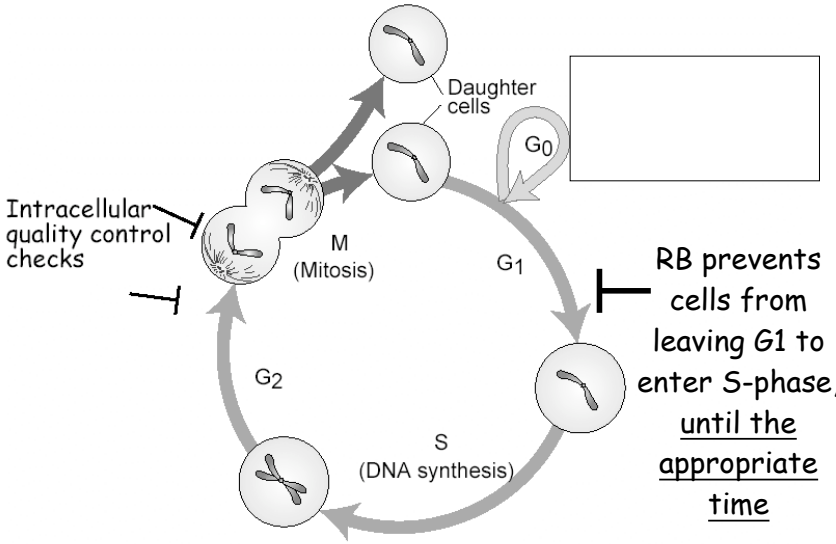
RB prevents cells from leaving G1 to enter S-phase, until the appropriate time

RB – the Retinoblastoma Gene – was the first example of a Tumor Repressor Gene (aka a Recessive Oncogene)



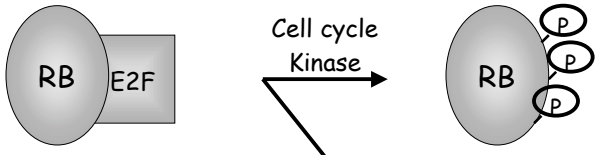


Loss of Function Mutations in both RB genes lead to malignant tumors of the retina during the first few years of life

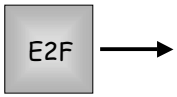


RB prevents cells from leaving G1 to enter S-phase, until the appropriate time

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

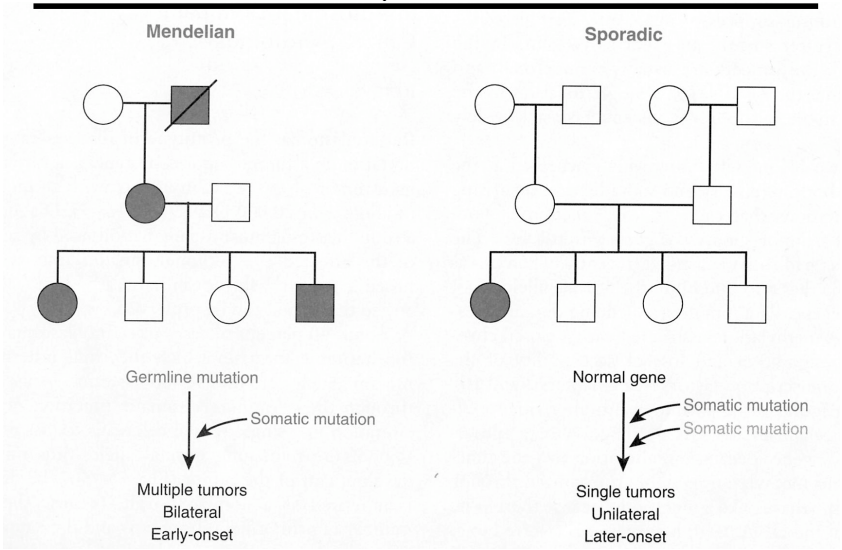


Must lose function of both RB alleles in order to lose cell cycle control

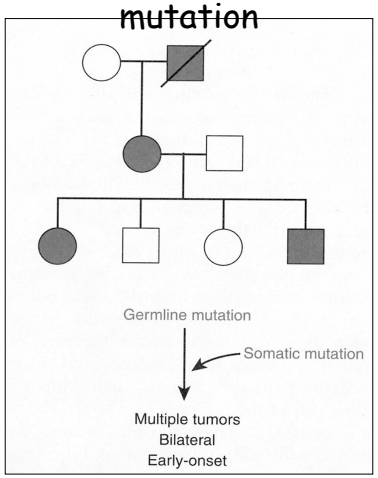


Transcribes genes for replication and cell proliferation

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

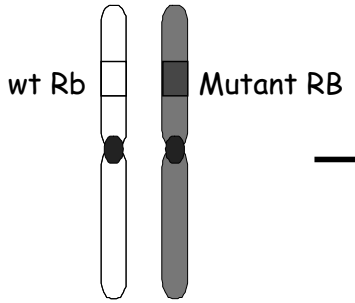


The Retinoblastoma disease behaves as an autosomal **dominant** mutation



- 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" hypthesis was proposed
- During development of the retina a second mutation is almost certain to occur
- RB is one of the very few cancers

How is the second RB allele rendered non-functional?

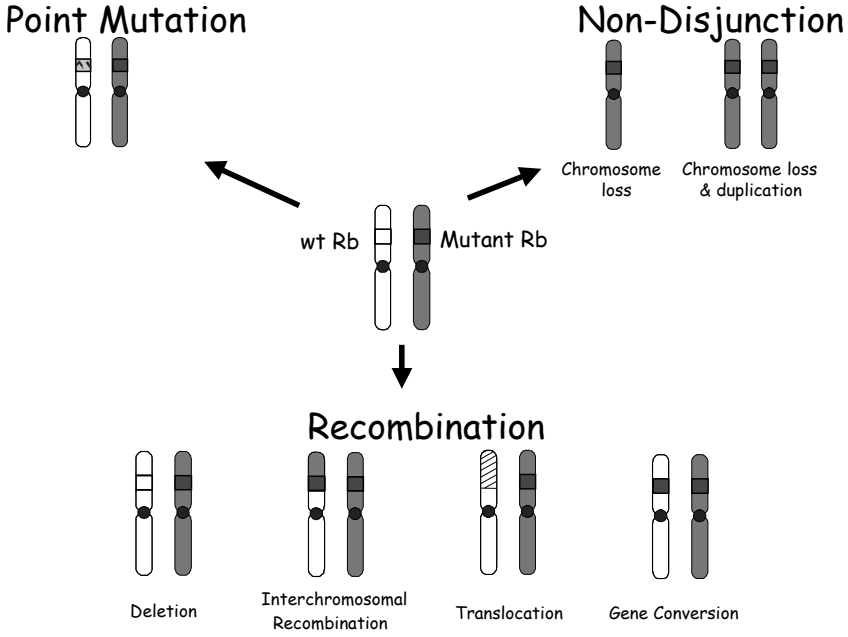


Heterozygous for RB mutation

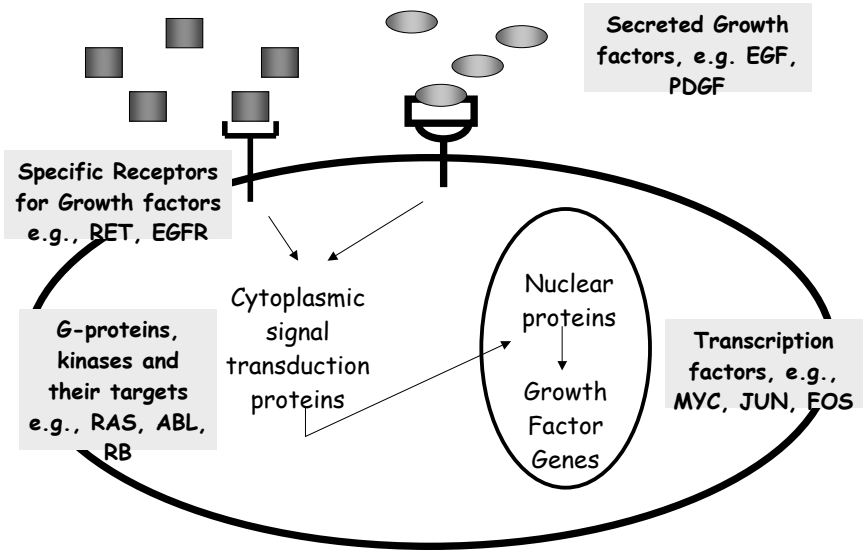
Loss of Heterozygosity

LOH

This can happen is several ways



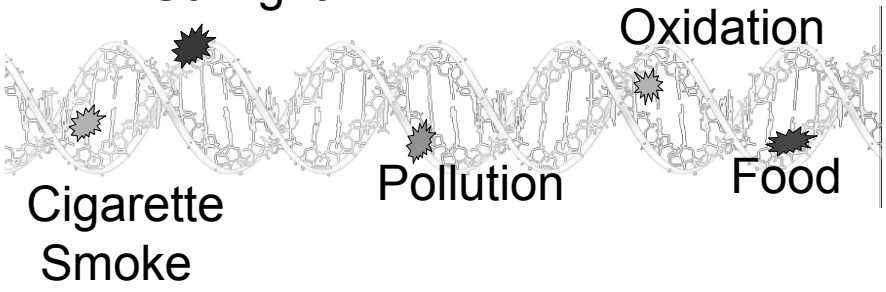
Signal Transduction and Growth Regulation

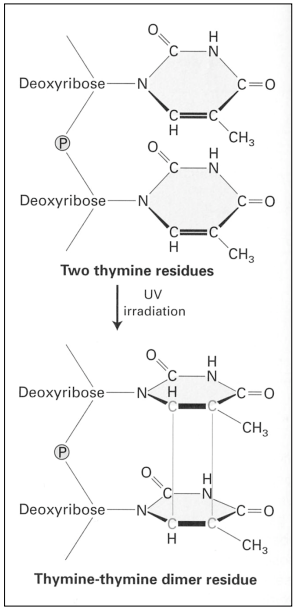


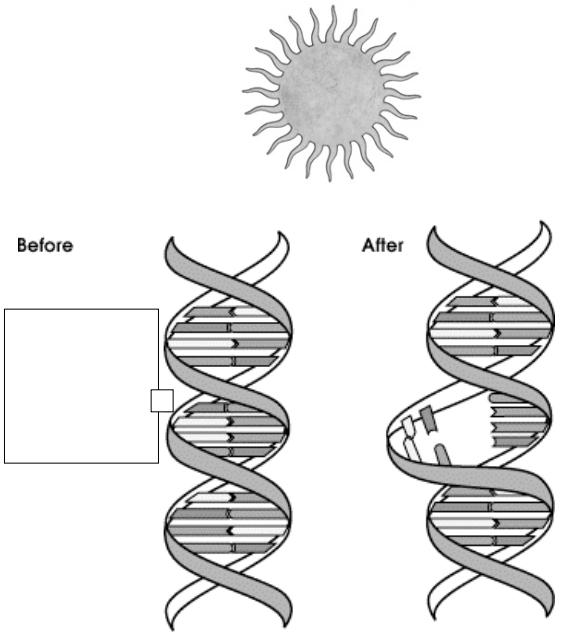
What chromosomal events convert proto-oncogenes to dominantly acting oncogenes and contribute to loss of tumor suppresor genes?

- Point mutations (e.g., RAS, Rb)
- Partial deletion mutations (e.g., RTKs)
- Chromosomal translocations that produce novel fusion proteins (e.g., Bcr-Abl)
- Chromosomal translocation to juxtapose a strong promoter upstream and the proto-oncogene such that it is inappropriately expressed (e.g., cMyc, Bcl2)
- Gene amplification resulting in overexpression (e.g., N-Myc)

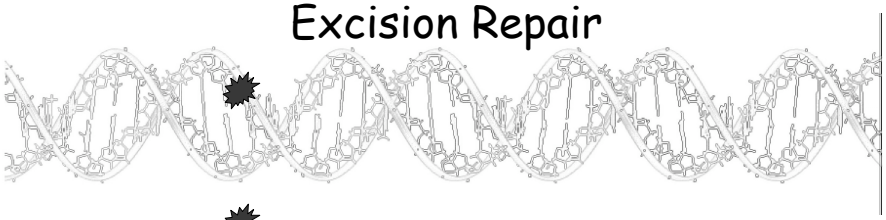
All of these mutational events are induced by natural and man-made environmental agents

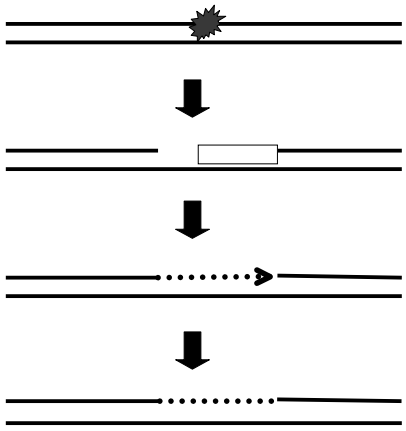






Excision Repair



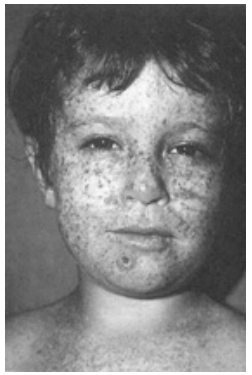


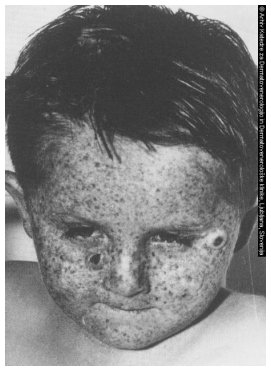
Proteins Detect Damage

Enzymes Excise DNA Segment with Damage

DNA Polymerase Copies the Undamaged Strand

DNA Ligase Seals the ends together





Xeroderma Pigmentosum An Autosomal Recessive Disease

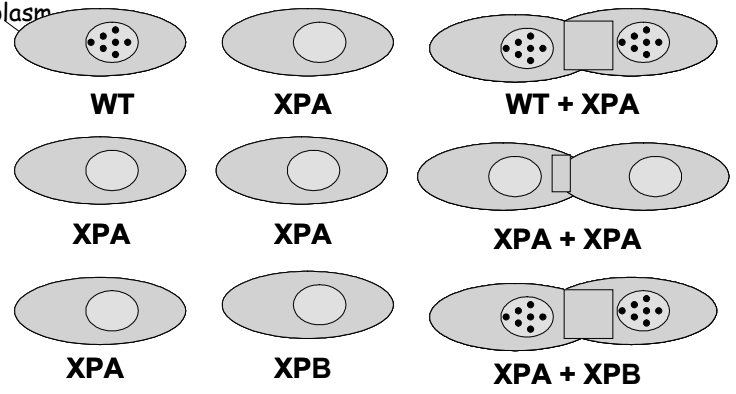
2000-fold increased risk of

Complementation in fused cells reveals 7 genes that cause Xeroderma Pigmentosum

nucleus = DNA Excision Repair after UV Irradiation

= No DNA Excision Repair after UV Irradiation

cytoplasm



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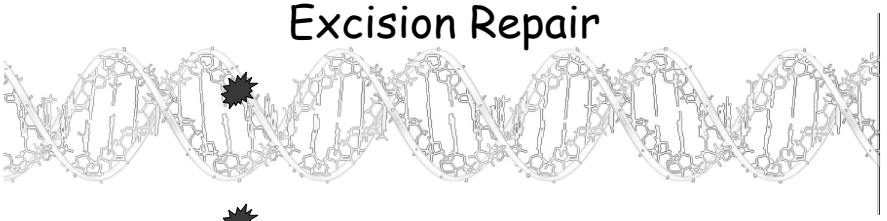

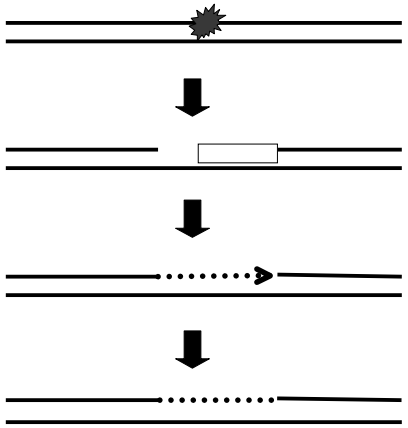

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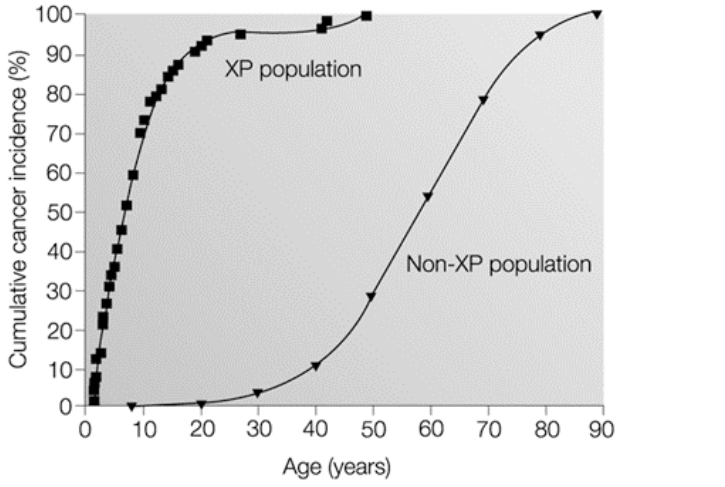
Age at First Skin Cancer



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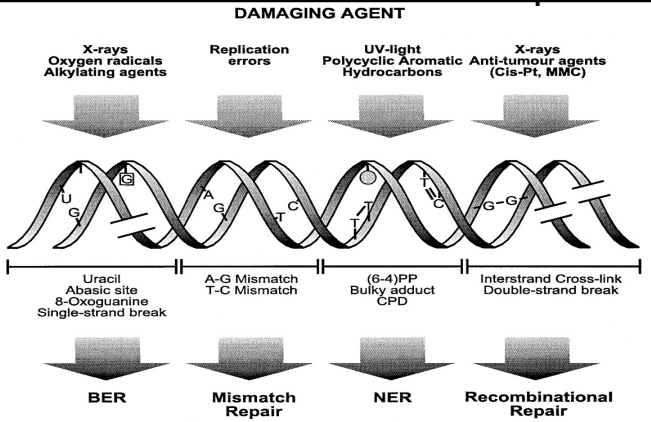
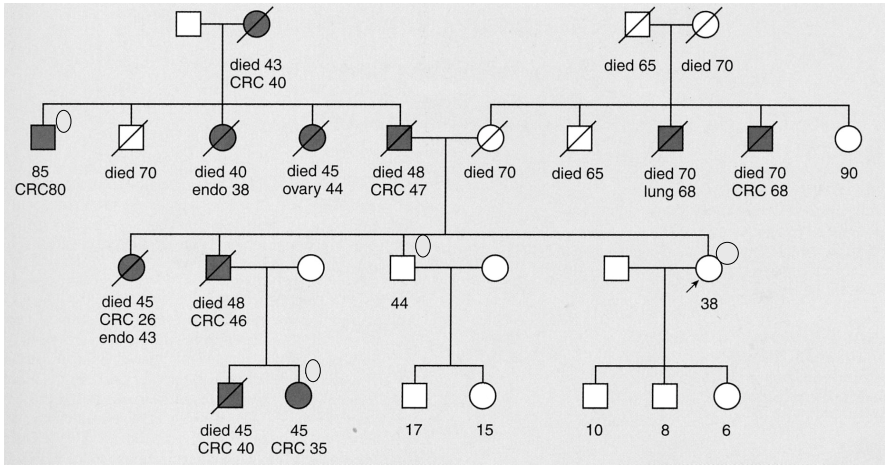
There are Many Other Human Cancer Prone Syndromes Deficient in DNA Repair



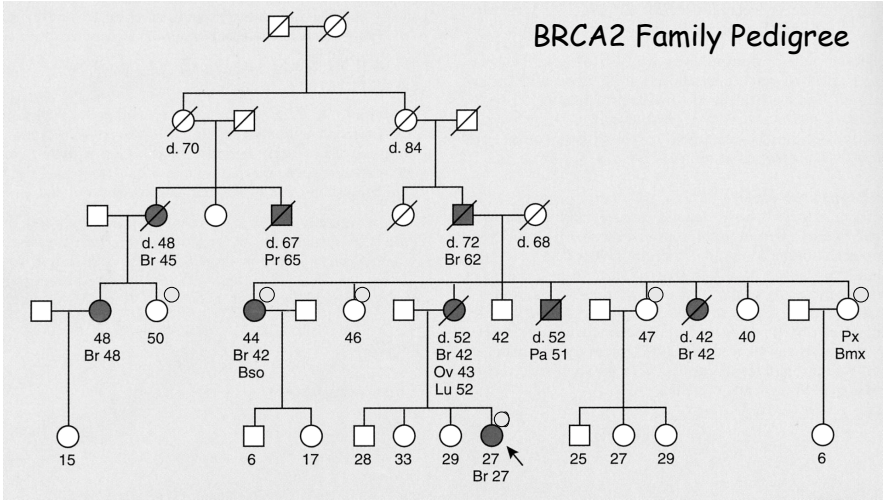
If DNA Repair pathway is defective →

BER	Mismatch Repair	NER	Recombinational Repair
Colon	Colon Ovary Endometrial	~~Skin~~	Breast Ovary Leukemias

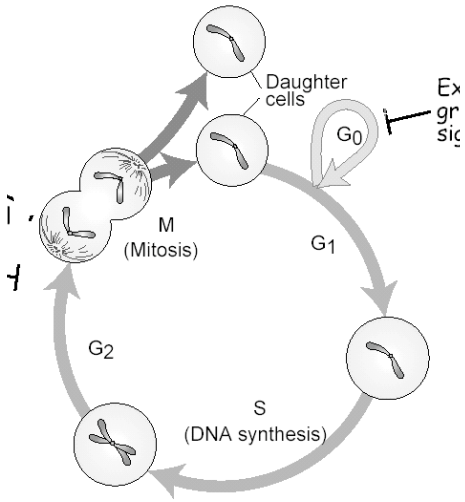
Hereditary Nonpolyposis Colon Cancer
DNA Mismatch Repair Defect
Syndrome inherited as Autosomal Dominant



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

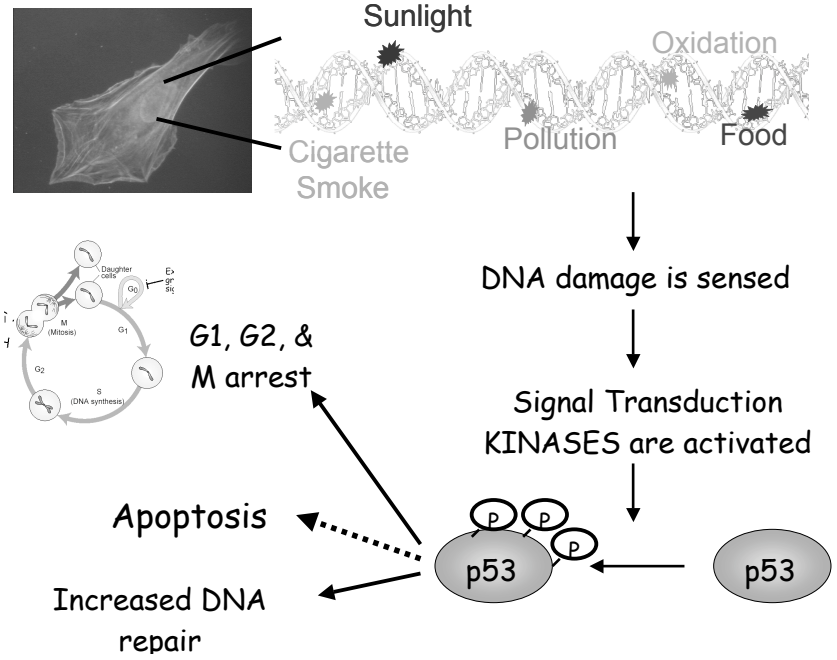


Cells need time to repair DNA: DNA Damage induces Cell Cycle Checkpoints



• DNA damage signals cell cycle check points

• If the damage is too great to fix by repair a signal is sent for the cell to undergo suicide i.e.,



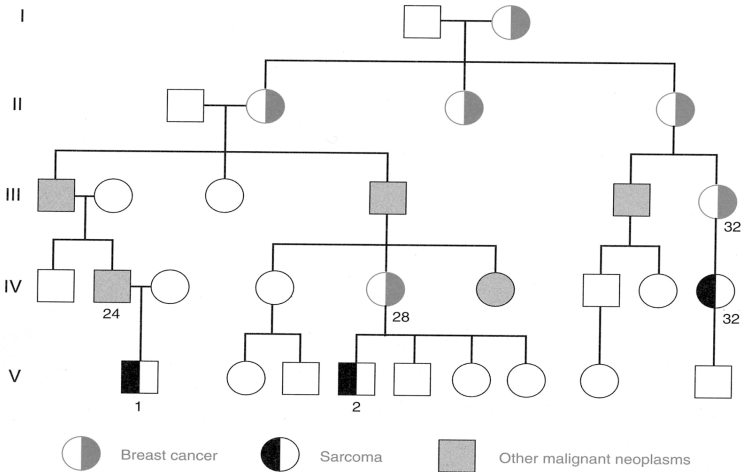
Loss of p53 function occurs in more than 50% of human cancers!!

- These cancer cells are genetically unstable because they are less able to do the following:

- Stop the cell cycling to allow time for DNA repair

- Carry out efficient DNA repair

Li-Fraumeni Syndrome – Inheritance of one p53 null allele



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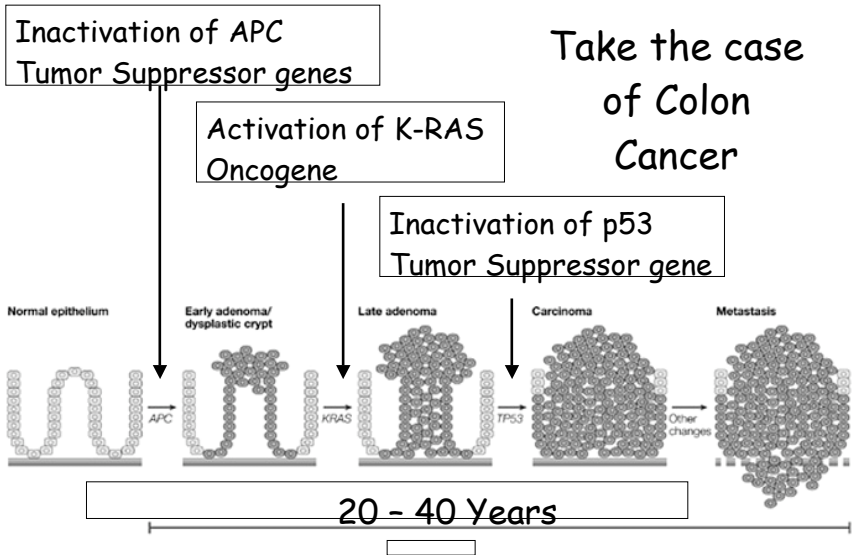
Most fully blown cancers require inactivation of tumor suppressor genes and activation of oncogenes



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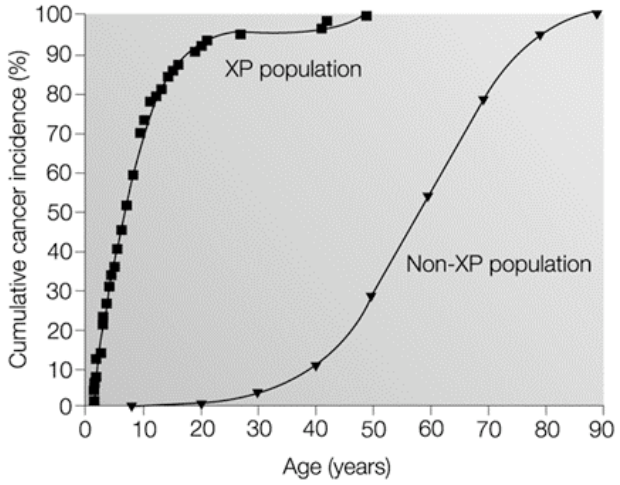

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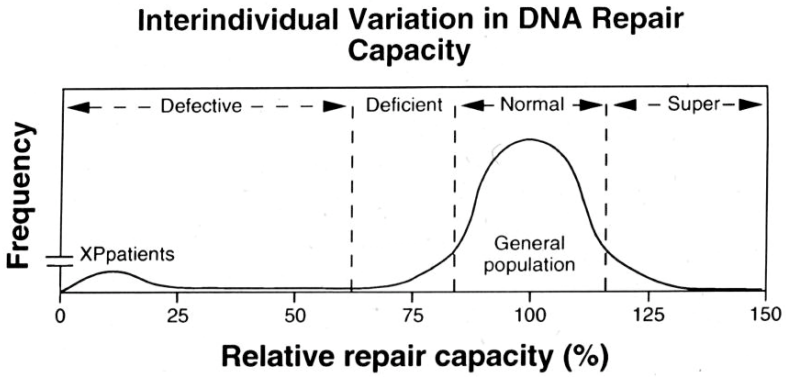
Xeroderma Pigmentosum ~ 1/250,000



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