

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

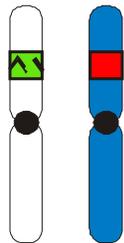
Mutator genes

Usually recessive, loss-of-function mutations
that increase spontaneous and environmentally
induced mutation rates

What chromosomal events convert proto-oncogenes to dominantly acting oncogenes

- Point mutations (e.g., RAS)
- 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)

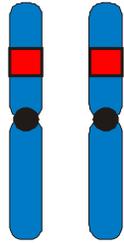
Point Mutation



Non-Disjunction

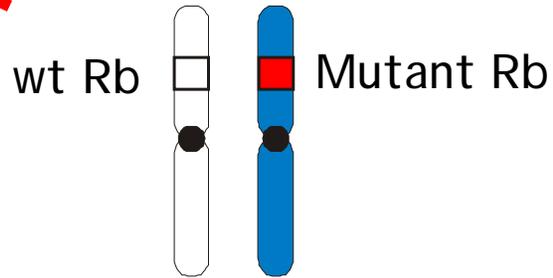


Chromosome loss



Chromosome loss & duplication

LOH - Loss of heterozygosity

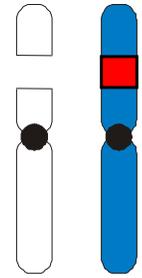


wt Rb

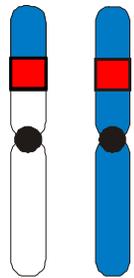
Mutant Rb



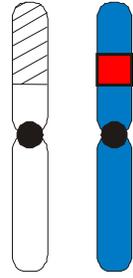
Recombination



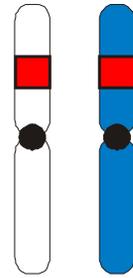
Deletion



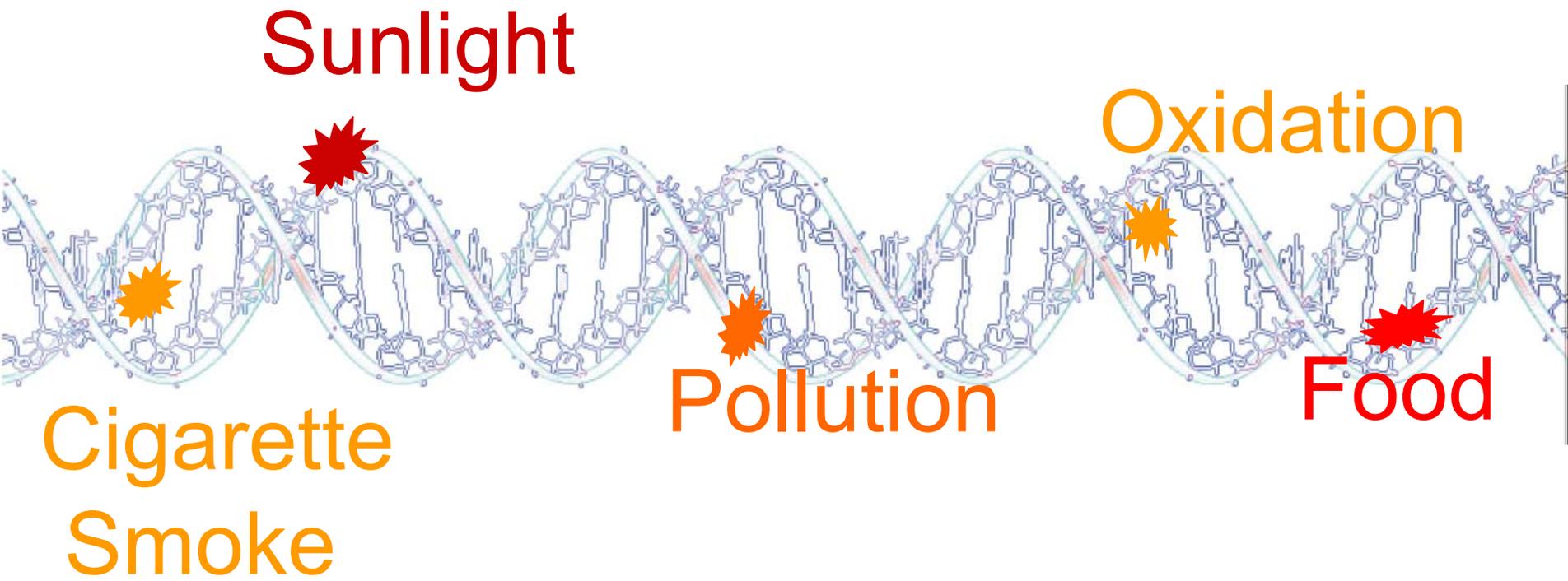
Interchromosomal Recombination



Translocation



Gene Conversion



Courtesy of Professor Bevin P. Engelward. Used with permission.

Excision Repair



Proteins Detect Damage



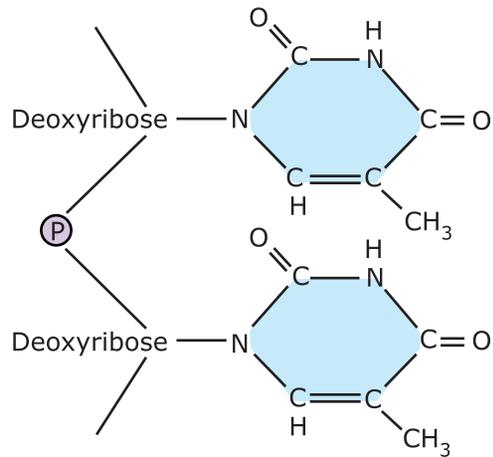
Enzymes Excise DNA Segment with Damage



DNA Polymerase Copies the Undamaged Strand

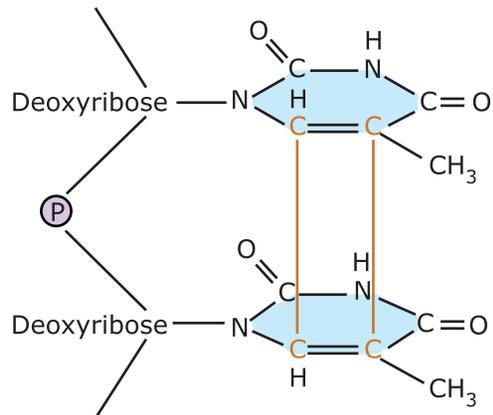


DNA Ligase Seals the ends together

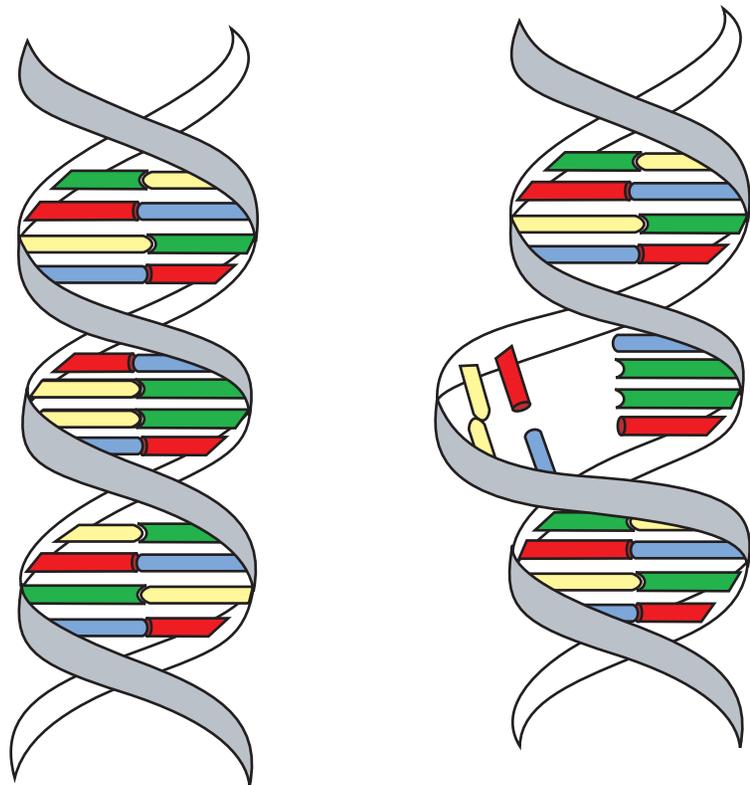
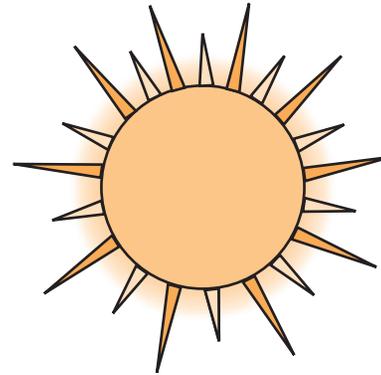


Two thymine residue

UV irradiation ↓



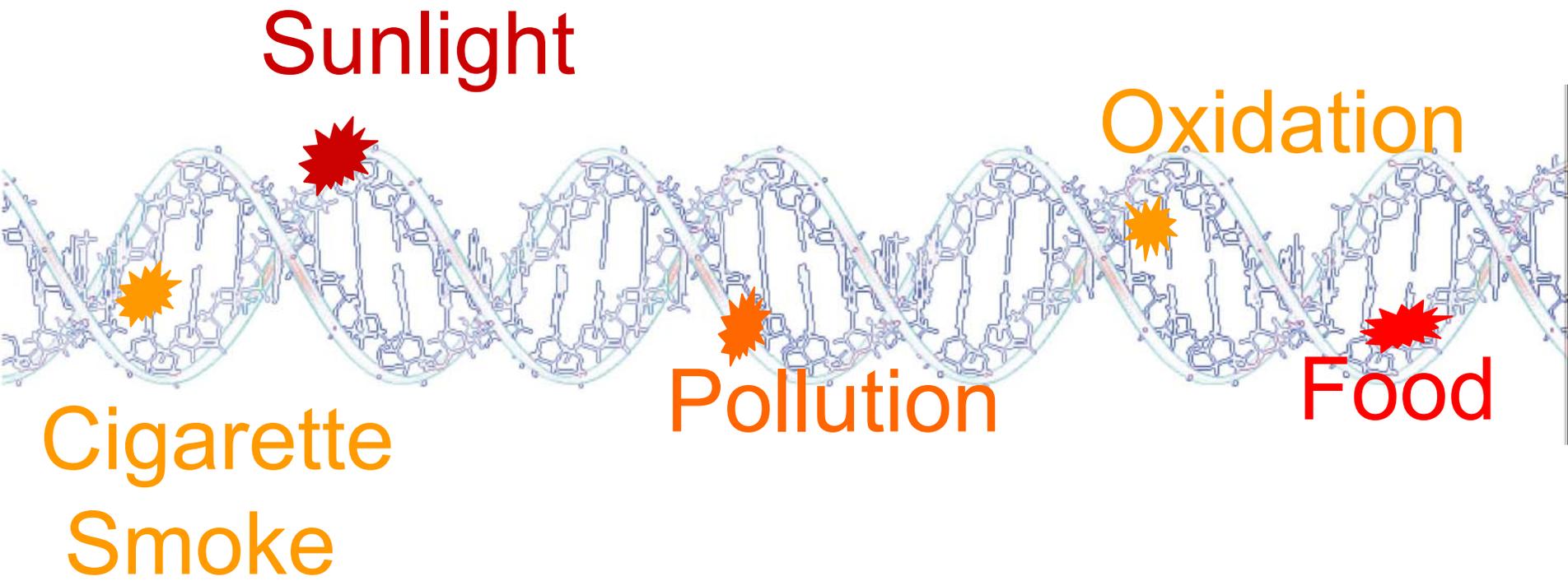
Thymine-thymine dimer residue



Before

After

Figure by MIT OCW.



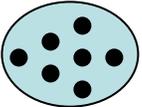
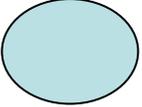
Courtesy of Professor Bevin P. Engelward. Used with permission.

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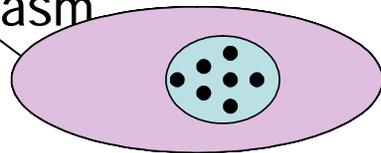
Xeroderma Pigmentosum An Autosomal Recessive Disease

2000-fold increased risk of
skin cancer

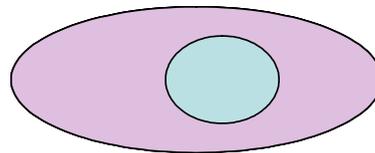
Complementation in fused cells reveals 7 genes that cause Xeroderma Pigmentosum

nucleus  = DNA Excision Repair after UV Irradiation
 = No DNA Excision Repair after UV Irradiation

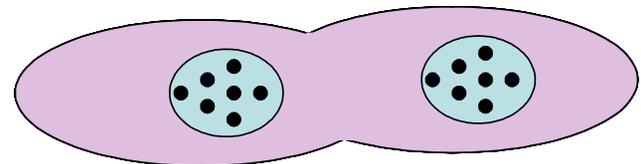
cytoplasm



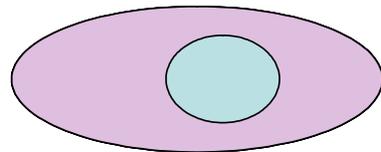
WT



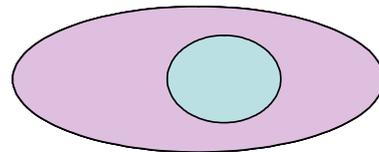
XPA



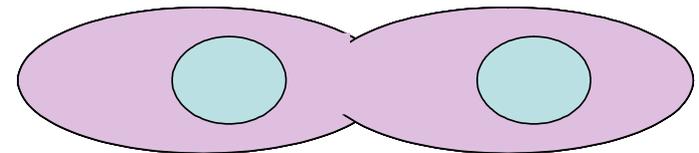
WT + XPA



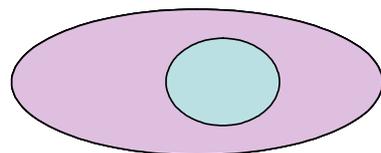
XPA



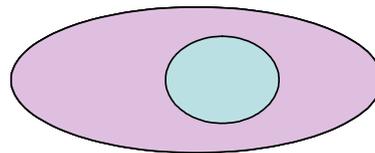
XPA



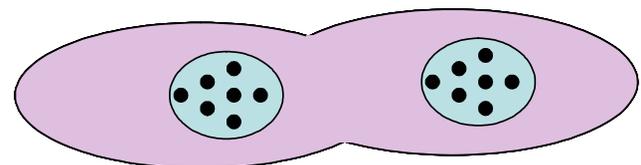
XPA + XPA



XPA



XPB



XPA + XPB

Age at First Skin Cancer

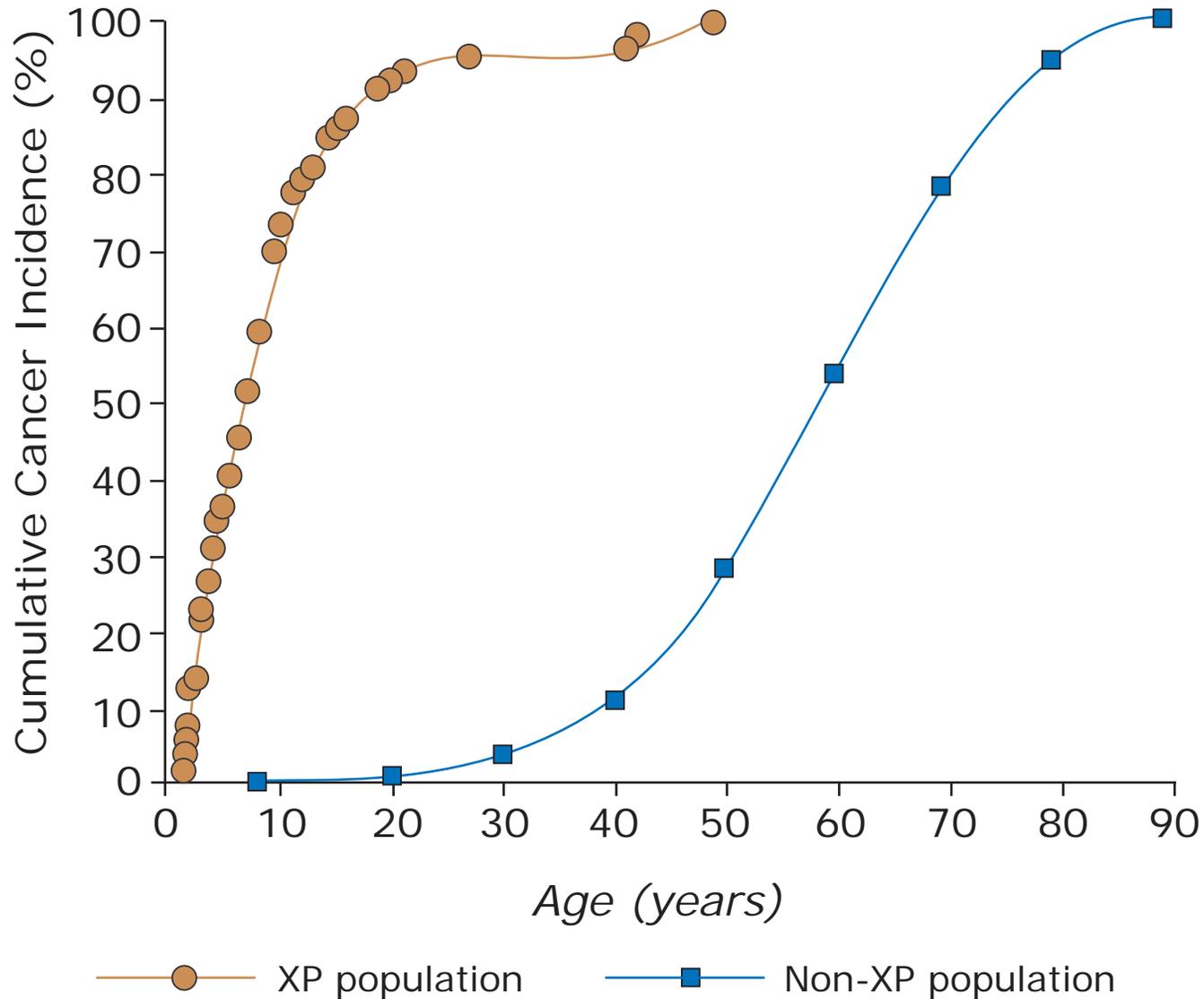


Figure by MIT OCW.

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

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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**

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Please see Lodish, Harvey, et. al. *Molecular Cell Biology*.
5th ed. New York : W.H. Freeman and Company, 2004.

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

BRCA2 Family Pedigree

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Please see Lodish, Harvey, et. al. *Molecular Cell Biology*.
5th ed. New York : W.H. Freeman and Company, 2004.

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

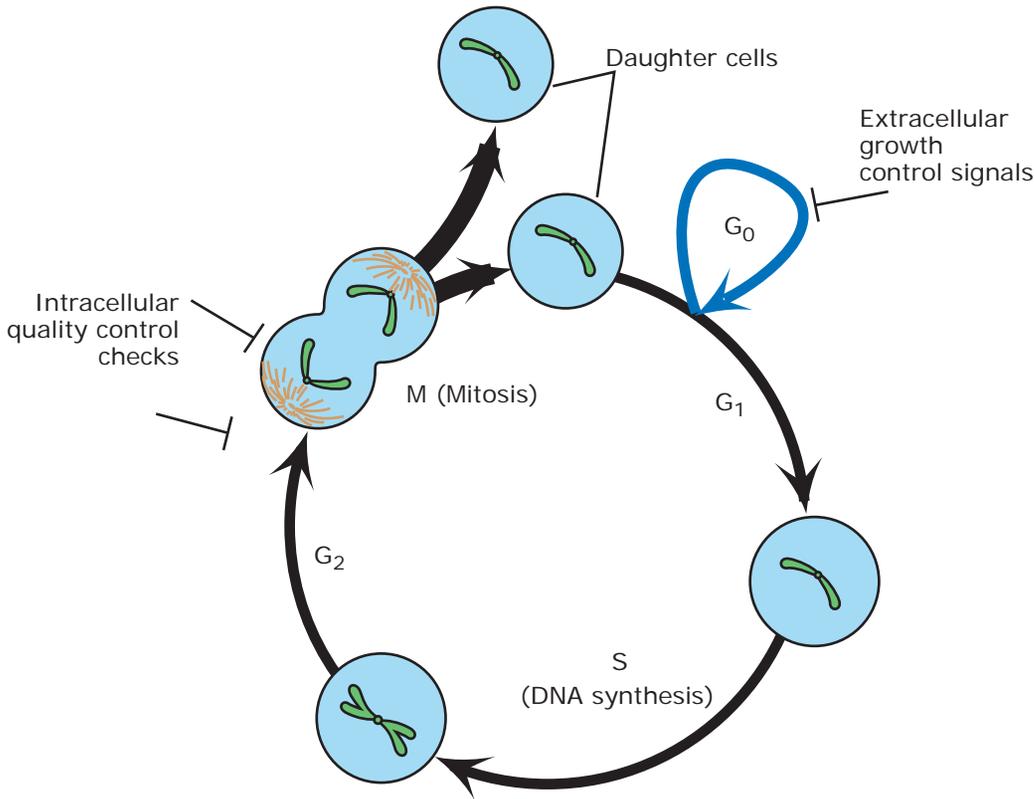
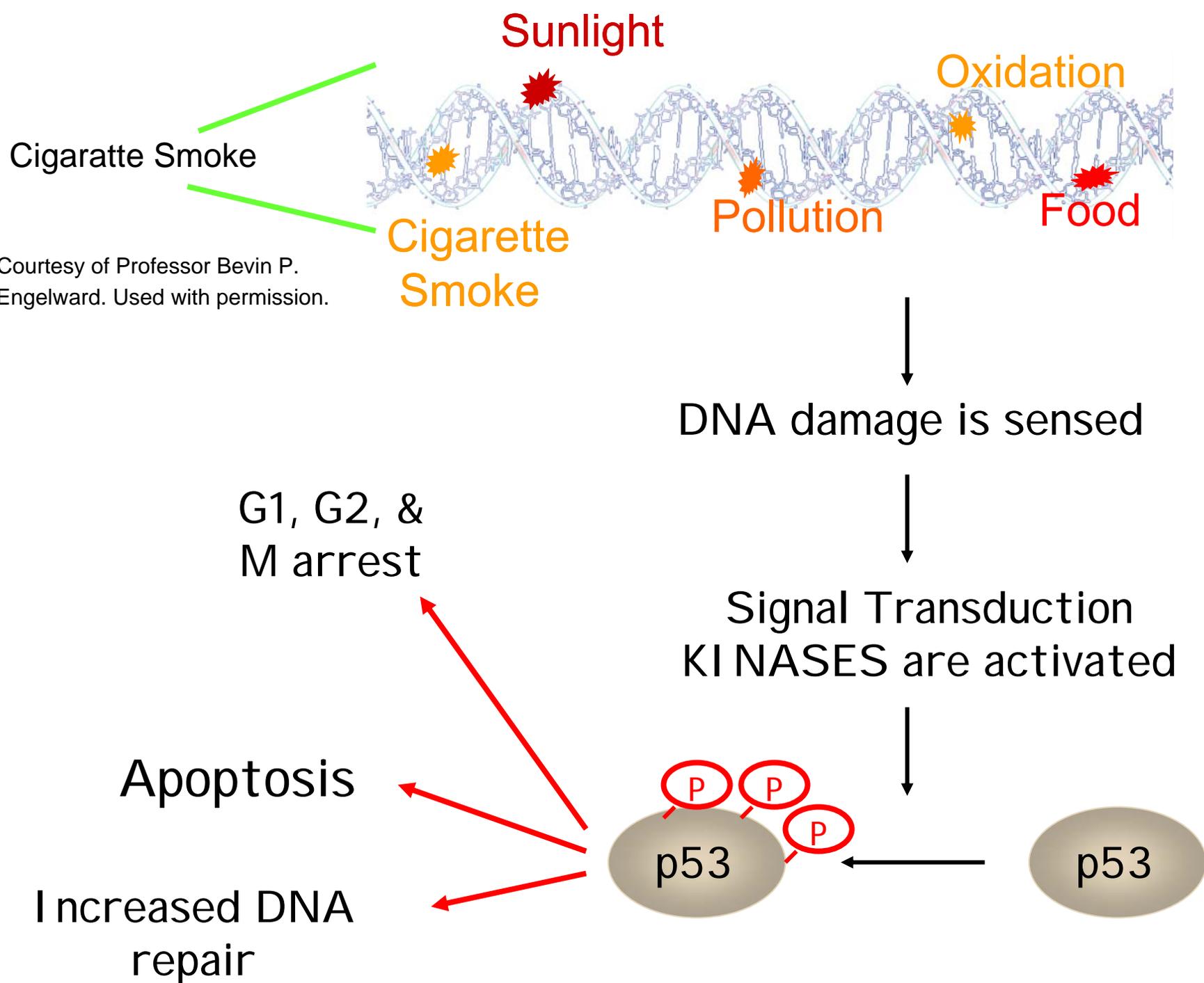


Figure by MIT OCW.

- 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



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

- These cancer cells are genetically unstable because they are **unable** to do the following:
 - Stop the cell cycling to allow time for DNA repair
 - Carry out efficient DNA repair
 - Undergo apoptosis

Li-Fraumeni Syndrome - Inheritance of one p53 null allele

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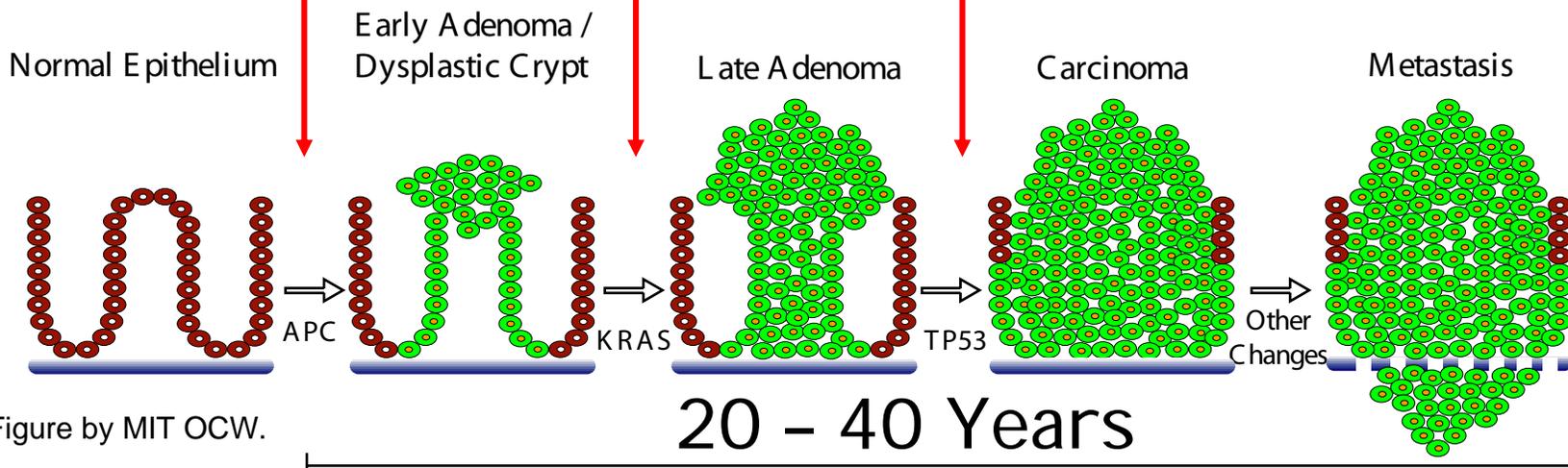
Most fully blown cancers require inactivation of tumor suppressor genes and activation of oncogenes

Inactivation of APC
Tumor Suppressor genes

Activation of K-RAS
Oncogene

Inactivation of p53
Tumor Suppressor gene

Take the case
of Colon
Cancer



Xeroderma Pigmentosum ~ 1/250,000

Image removed due to copyright reasons. Please see Wei et al., Clinical Chemistry, Vol. 41, No. 12, 1995.

Good Luck for the Final Exam