Molecular Disease Mechanisms

Lecture 2: Genotoxic Carcinogenesis

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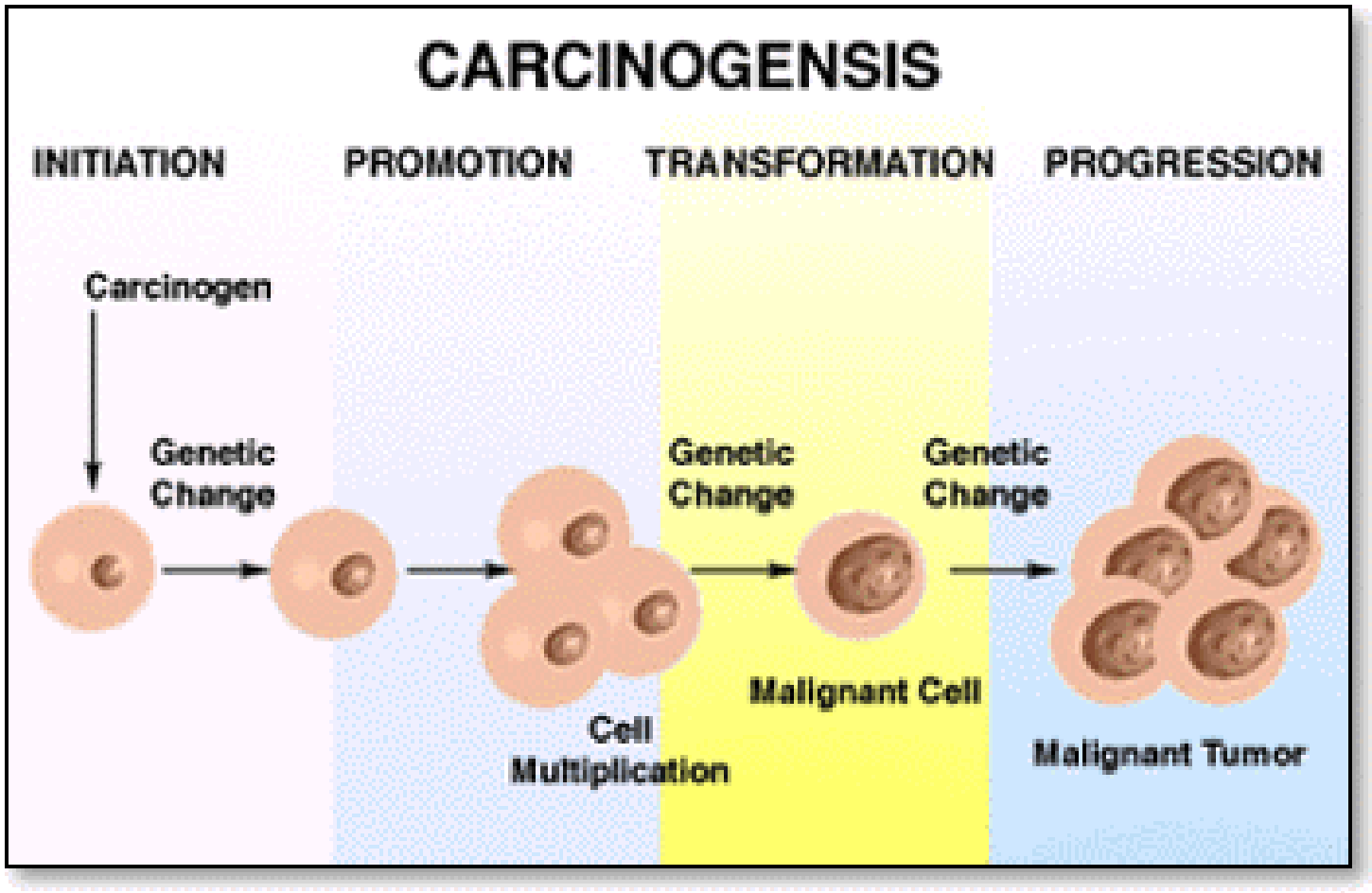


-Multi-step process…

-Xenobiotic – chemical substance not naturally produced by an organism

Carcinogenesis

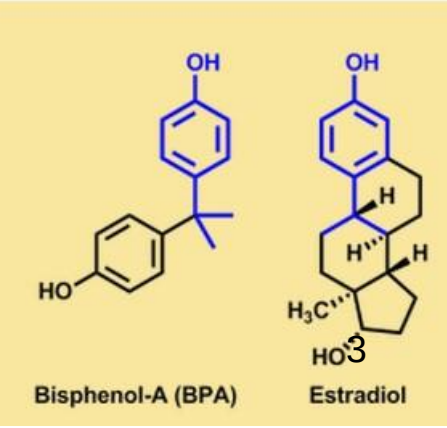
- Genotoxic
- Direct reaction with DNA to alter its structure
- *Direct carcinogens:*
- No metabolic activation (alkylating agents)
- *Indirect carcinogens:*
- Require metabolic activation (aromatic amines, PAHs)

- Non-Genotoxic
- Don't directly cause DNA mutation
- Increased cell proliferation
- Decreased apoptosis
- Induction of metabolic enzymes

Example:

endocrine

disruptors



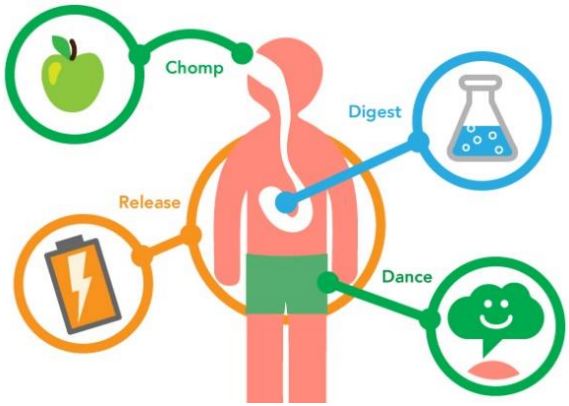
Some Major Examples of Genotoxic Carcinogens

- UV Radiation
- Reactive Oxygen Species
- Polycyclic Aromatic Hydrocarbons (PAHs – Benzo[a]pyrene)
- Mycotoxins/Aflatoxins
- Acrylamide
- alkenes and haloalkanes
- Aromatic amines
- Furans
- Polycyclic Aromatic Amines
- N-Nitrosamines

Lecture 2 Topic Outline

Genotoxicity

1. Role of metabolism in carcinogenesis
2. DNA Damage (DNA adducts)
3. Mutagenesis (Translesion DNA synthesis)
4. DNA Repair

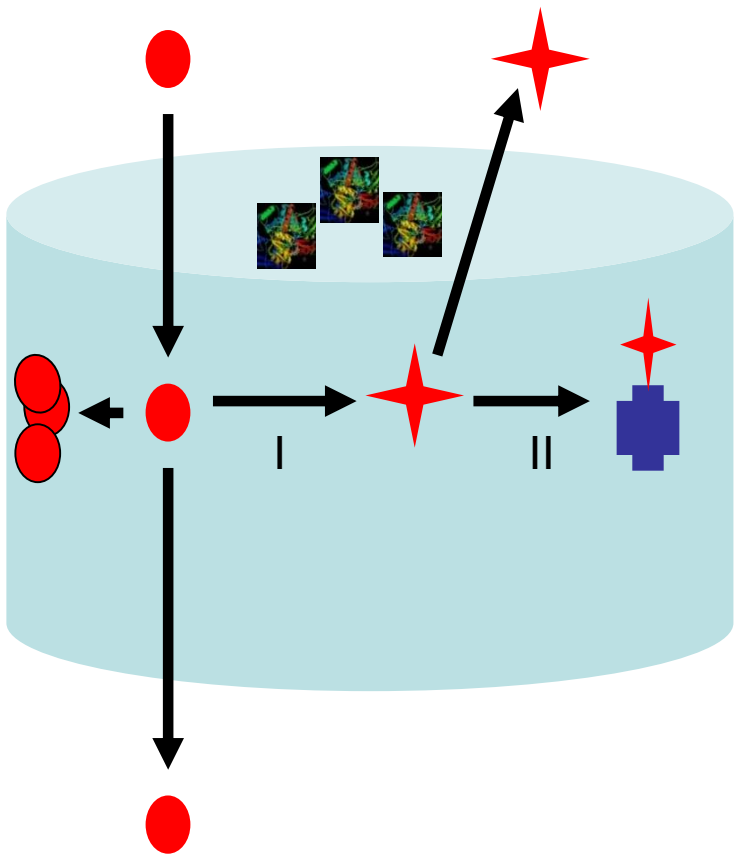


Lecture 2, Part 1

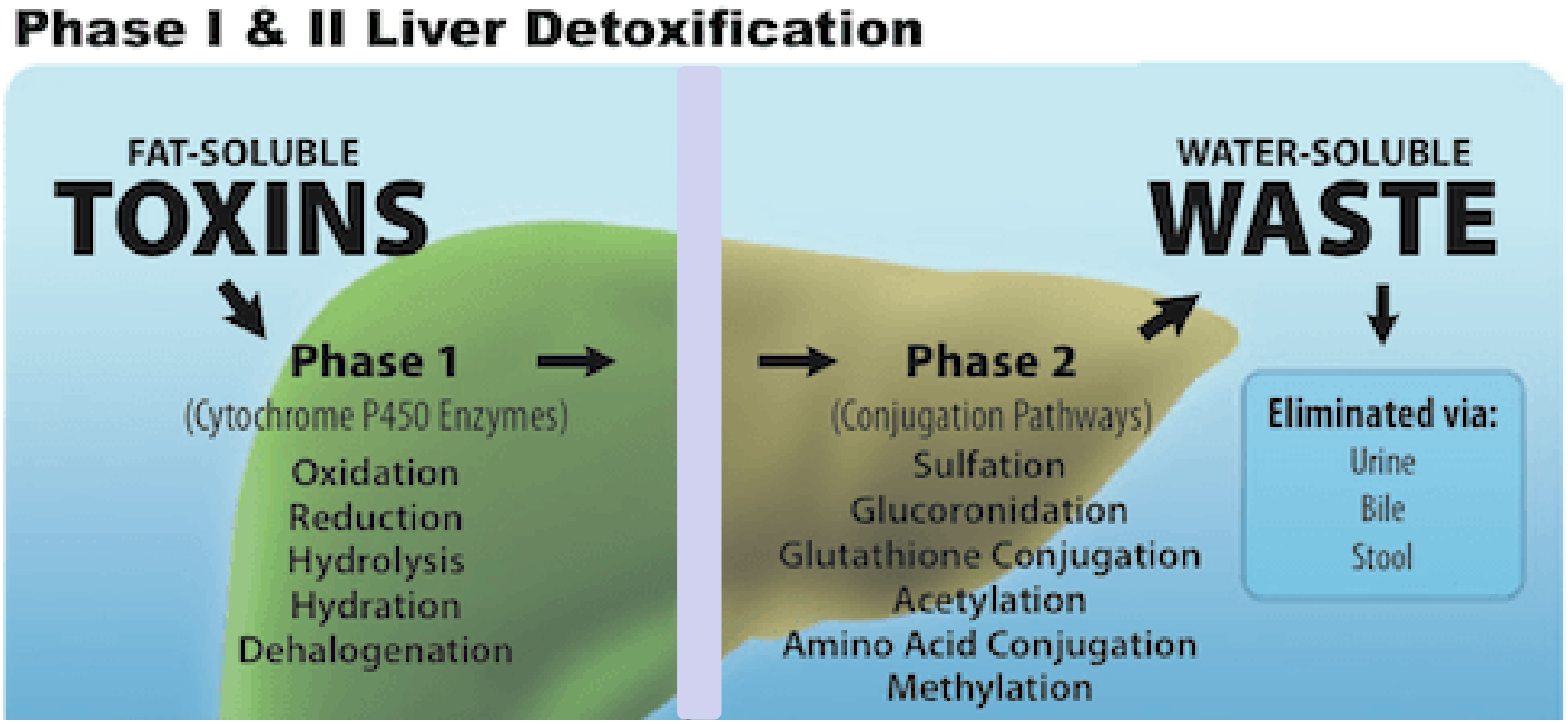
ROLE OF METABOLISM IN CARCINOGENESIS

Concepts in Xenobiotic Biotransformation

- Change in physical properties → increase in hydrophilicity
- Metabolites as biologically reactive intermediates
- Enzyme levels depend on tissue type
- High polymorphism

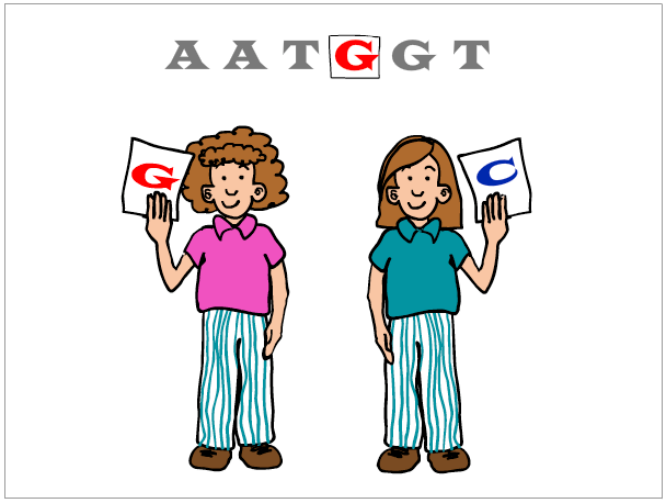


Xenobiotic biotransformation



Mutation vs Polymorphism

- Both are DNA sequence variations
- A mutation is any change in a DNA sequence away from the normal, ie implying there is a normal allele prevalent in the population and that mutations are rare and are an abnormal variant
- A polymorphism is a DNA sequence variation common in the population
  - No single allele is regarded as the standard sequence
  - Most polymorphic variants do not overtly cause a disease, impact characteristics like height, rather than disease
  - Many are neutral in effect
  - Some contribute to disease susceptibility and influence drug responses

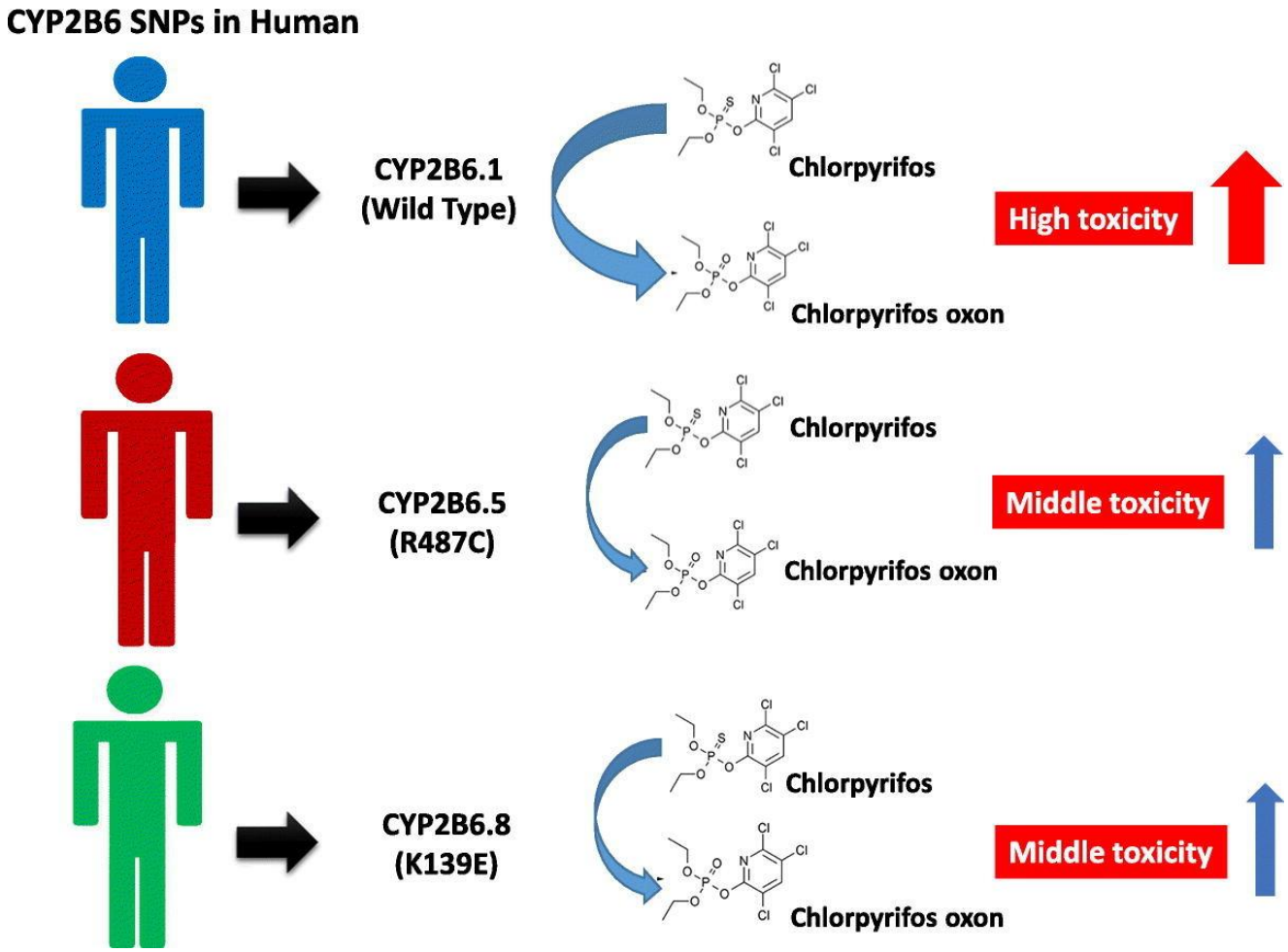


i.e. high polymorphism in metabolic enzymes

Metabolic Enzyme Polymorphism in Cancer Susceptibility

- Considerable inter-individual genetic variability in metabolic pathways
- Why is it important to understand?
  - Identification of people at increased risk (association of genetically determined variants with risks of carcinogenesis)
  - Personalized cancer prevention/therapy
- Molecular genetic basis of differential enzyme activities involved in metabolism

CYP2B6 has been identified in the human brain, the critical site in CPS poisoning

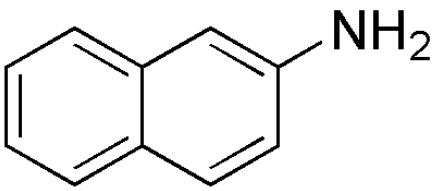


Allele CYP2B6.5 occurs more often in German people (10.9% of alleles) than in Japanese people (1.1% of alleles)

Genetic Polymorphism and Carcinogenesis, An Example:

Increased Risk for Male Bladder Cancer among a Cohort of Male and Female Hairdressers from Geneva. *Int. J. Epidemiol. (1985) 14 (4): 549-554.*

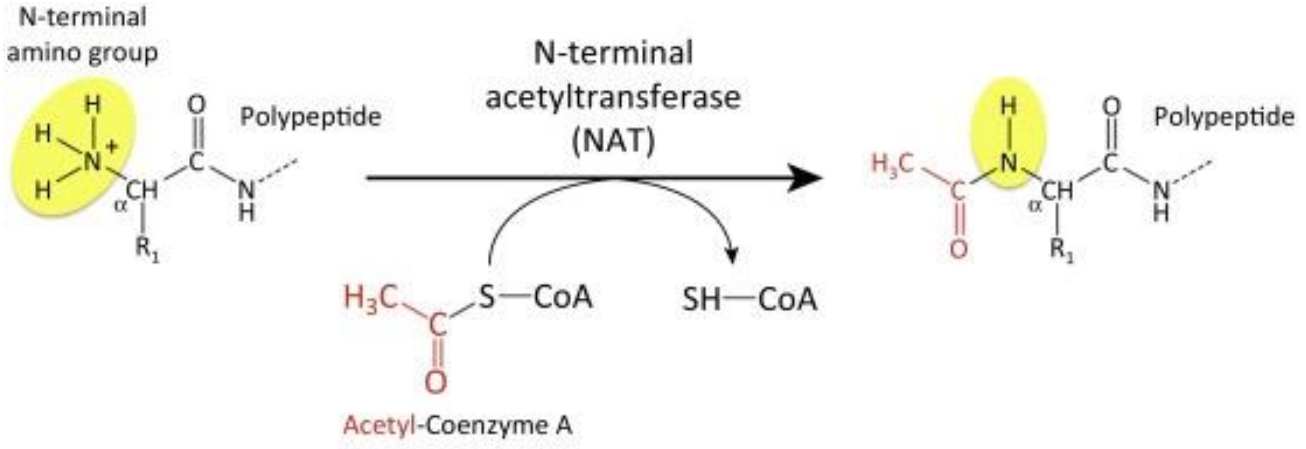
- Followed 703 male hairdressers born from 1880 onwards, who started salons in Geneva 1900-1964
- Mortality from 1942-1982 analyzed
- 10 bladder cancer deaths (~4 expected)
- Significant increase in all cancers
- Proposed link to colouring agents in hair gels widely used in men's hairdressing in the period



2-Naphthylamine

Bladder cancer susceptibility is modulated by *N*-Acetyl Transferase NAT Polymorphism

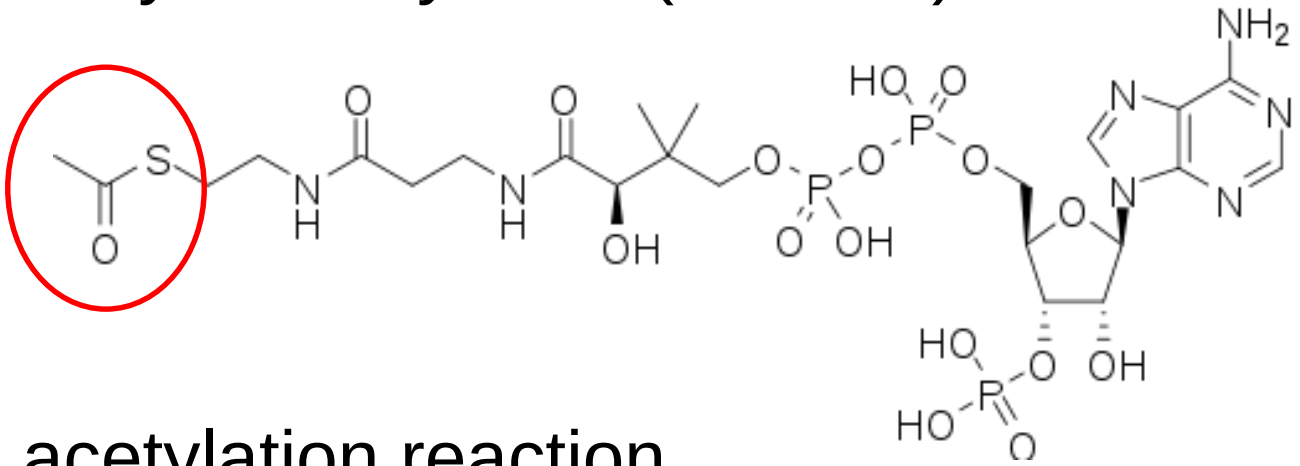
- Evidence for **polymorphism** and myeloma, lung, bladder, lymphoma, liver, colorectal cancer
- Associations between NAT **enzyme activities** and cancer risk
- NATs are involved in the metabolic activation and detoxification of arylamines



Trends in Biochemical Sciences

NAT Enzyme Characteristics

- Located in the cytosol
- Prevalent in liver in mammals
- Cofactor: acetyl-coenzyme A (Ac-CoA)



- Catalyzes acetylation reaction
- 2 well-characterized human variants
  - NAT1 and NAT2

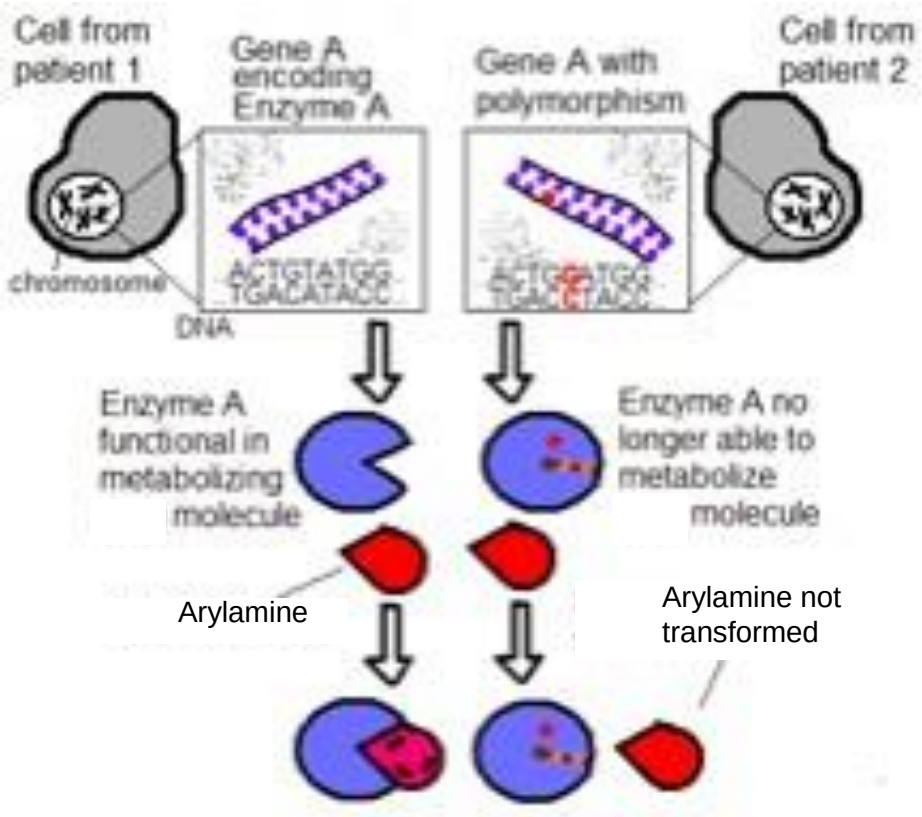
Action of NATs on Arylamines (AAs)

1. Detoxification
   - N-acetylation
2. Activation
   - N-hydroxy AAs by P450s
   - NATs catalyze the formation of N-acetoxy esters of N-hydroxy AAs
   - N-acetoxy esters cleave to yield reactive nitrenium
   - Nitrenium is potent DNA alkylating agent

Aryl amine metabolism and bladder cancer

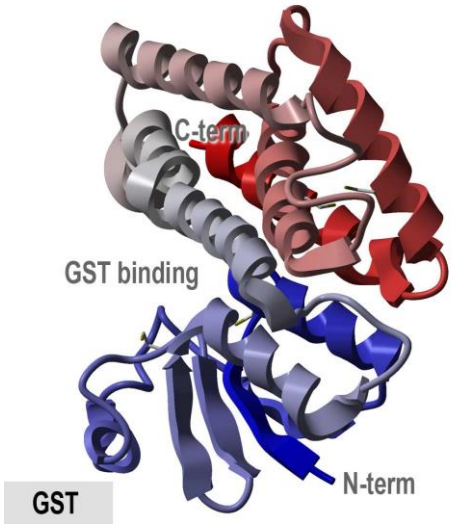
Genetic Polymorphism in NATs

- Extensive polymorphisms with high frequency
- Segregate human population into rapid, intermediate, and slow acetylator phenotypes
- Slow acetylators exhibit increase in risk of developing several cancers, including bladder cancer, as compared with rapid acetylators
- Inter-individual differences and ethnic group-based differences

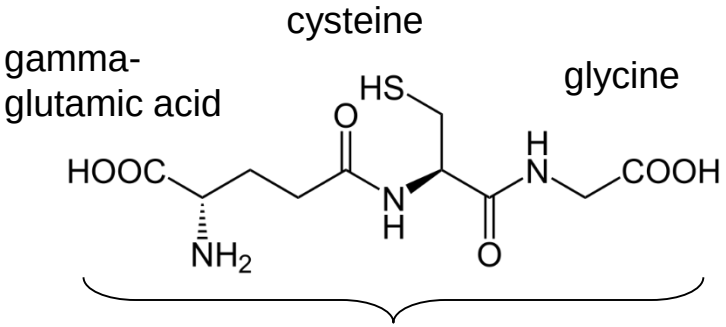


Adapted from pharmacogenomics figure
http://www.jyi.org/wp-content/uploads//img1102.jpg

GST polymorphisms associated with elevated cancer risk



http://en.wikipedia.org/wiki/Glutathione_S-transferase

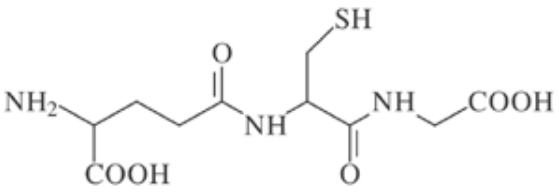


GSH

Tripeptide

- GSTs are large multigene family of enzymes involved in detoxification of potentially genotoxic chemicals
- conjugation of the reduced form of glutathione (GSH) to xenobiotic substrates for detoxification
- high concentrations in liver, intestine, kidney
- Account for ~10% of cellular proteins

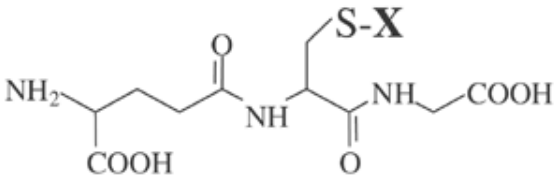
GST-mediated reaction



Glutathione

+ Xenobiotic (X)

GST



Glutathione-S-Conjugate

Detoxification

Human Glutathione Transferase Enzymes

GST Family	Class	Gene	Examples
Cytosolic	Alpha	GSTA1,GSTA2... GSTA5	GST A1-1
	Mu	GSTM1….GSTM5	GST M1-1
	Pi	GSTP1	GST P1-1
	Sigma	PGDS (prostaglandin synthase)	GST S1-1
	Theta	GSTT1	GST T1-1
	Zeta	GSTZ1	GST Z1-1
	Omega	GSTO1	GST O1-1
Mitochondrial	Kappa	GSTK1	GST K1-1

Example of Association Study: Glutathione S-transferase M1, T1, P1 genotypes and risk for development of colorectal cancer

- Tested relationship of GSTM1, GSTT1, and GSTP1 genes polymorphism, cigarette smoking and colorectal cancer incidence
- 181 patients with colorectal cancer and 204 controls
- DNA extracted from blood
- polymorphisms determined by PCR
- regression analysis → odds ratios (OR)

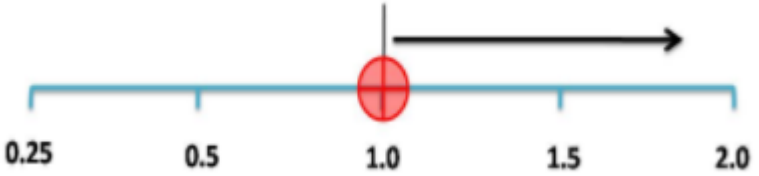
GSTM1 & GSTT1 Polymorphisms

OR for CRC: 1.62 & 1.64

GSTT1 Polymorphism

OR for CRC: 2.44 – in smokers

An OR greater than 1 indicates a higher risk of the disease in those exposed to the risk factor.



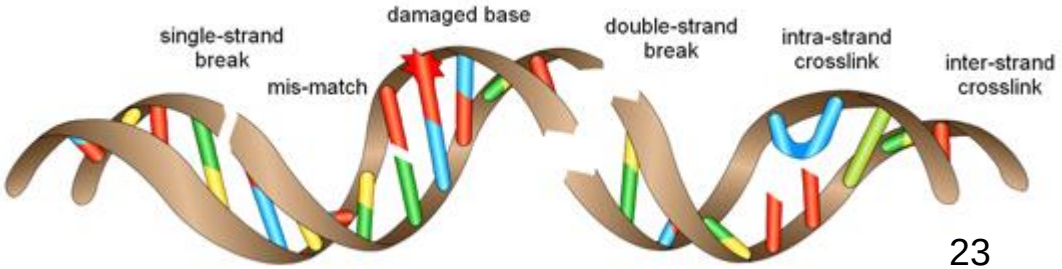
Biochem Genet. 2005 Apr;43(3-4):149-63.

Role of Metabolism: Key Points

1. Genotoxic carcinogens can be metabolized/biotransformed to proximal carcinogens
2. Proximal carcinogens are forms that chemically react with DNA and damage it
3. This form of DNA damage is a precursor to mutations
4. Genetic variability in metabolism/biotransformation enzymes can influence susceptibility to the harmful effects of genotoxic carcinogens
5. If the variant is associated with increased detoxification, the individual has a lower risk, and vice versa
6. We examined two important examples involving the polymorphic metabolism enzymes NAT and GST.
   - What transformations do they catalyze?
   - Do the transformations involve activation or detoxification or both? If both, how is the balance shifted toward cancer?
   - What cancers are this relevant for? Thus, what cancers are those carcinogens associated with?

Lecture 2, Part 2

DNA DAMAGE/DNA ADDUCTS



HOW FREQUENT IS DNA DAMAGE ?

Modification	Number*
8-Oxoguanine	~ 1000
Thymine glycol	~ 500
3-Methyladenine	~ 600
7-Methylguanine	~ 4000
O^6-Methylguanine	~ 200
Abasic site	~ 9000

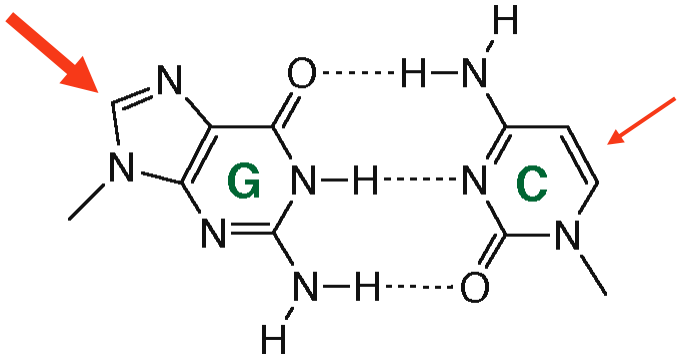
- *Number of residues generated daily per human genome
- Adduct levels for many potent genotoxins are well below these numbers

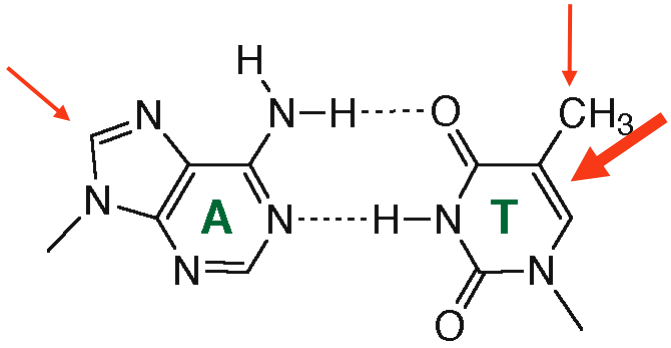
Kunkel *Trends Genet* **15**, 93 (1999)

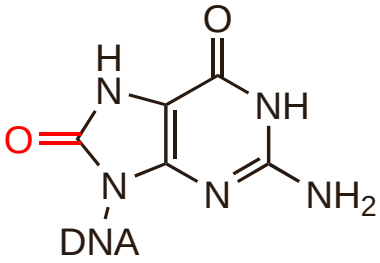
Common Reactions Yielding DNA Adducts

- Oxidation
- Hydrolysis
- Photodimerization
- Alkylation
  - Methylation Adducts
  - Other Bulky Alkylation Products

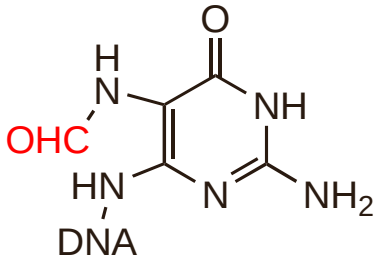
OXIDATIVE DAMAGE TO THE DNA BASES



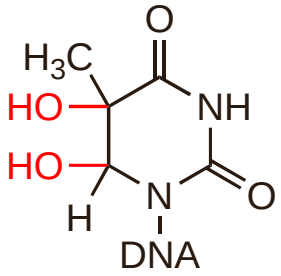




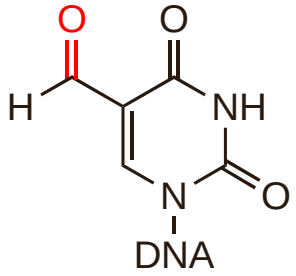
8-Oxoguanine (G)
mutagenic (G->T)



FormAmidoPYrimidine (G)
replication block

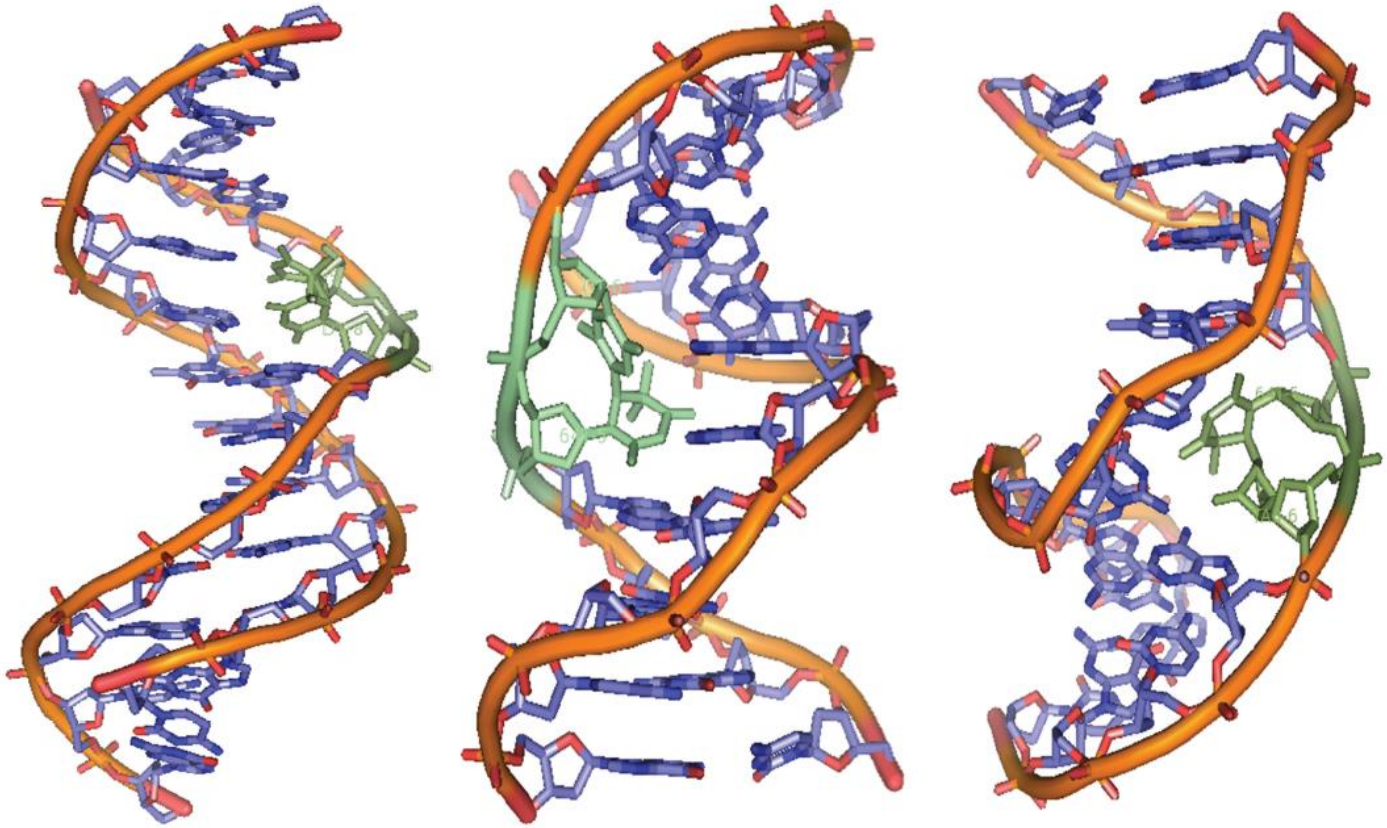


Thymidine glycol (T)
replication block



5-Formyluracil (T)
mutagenic (A->C,G)

DNA Photolesions induced by UV Distort the DNA double helix

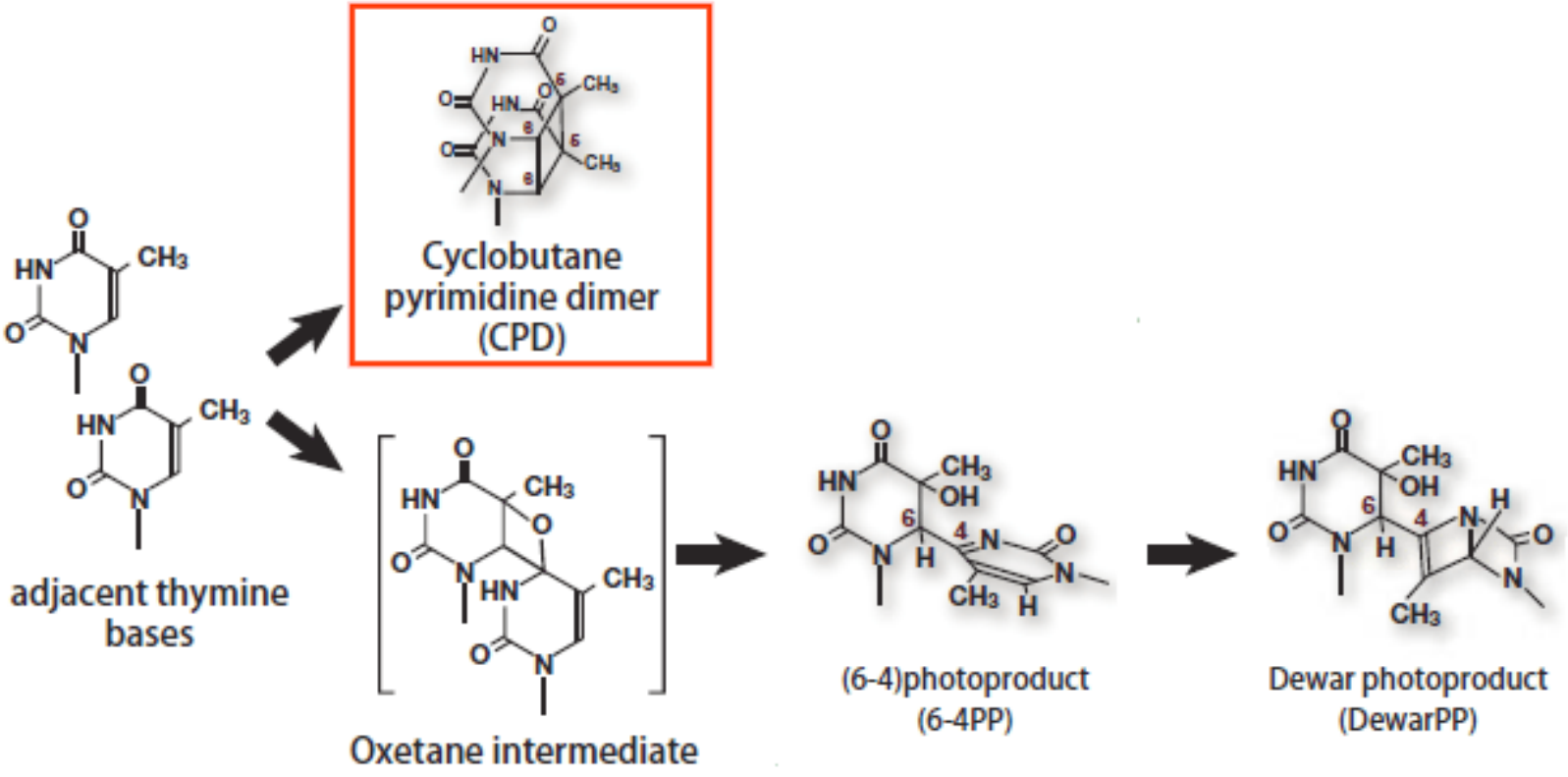


CPD (6-4) PP (6-4) Dewar Dimer

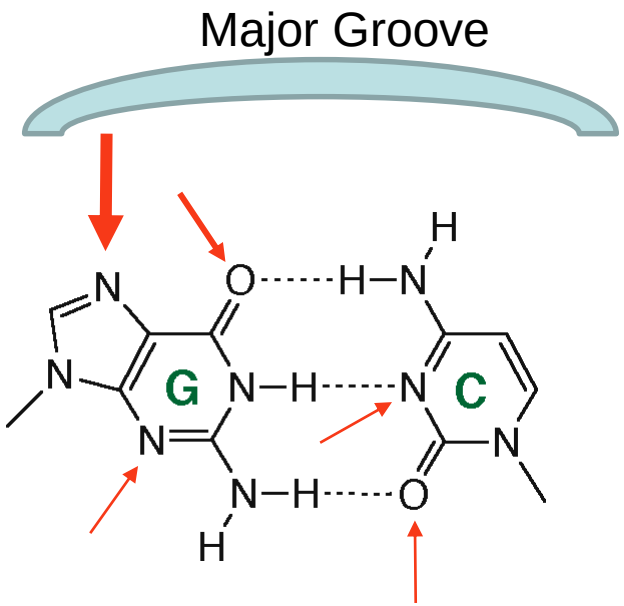
Large distortion of the DNA backbone

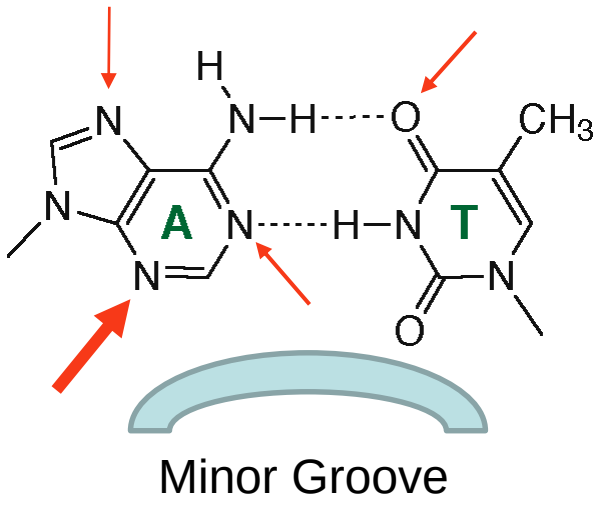
Rastogi, R. *et al*. J. Nuc. Acids. 2010. 2010, 32

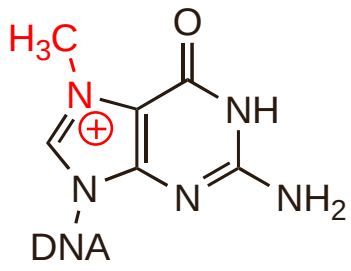
UV-associated DNA damage structures



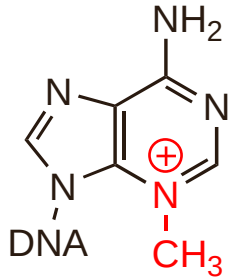
FREQUENT SITES OF ALKYLATION IN DNA



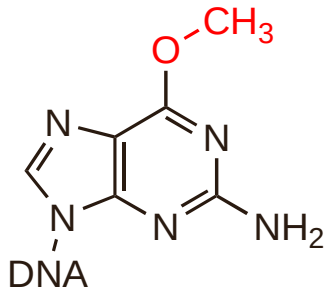




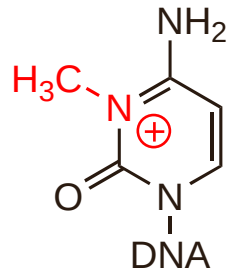
7-Mehtylgunanine (G)
relatively harmless



3-Mehtyladenine (A)
replication block



***O*^{6}-Mehtylguanine** (G)
replication block
mutagenic (G->A)

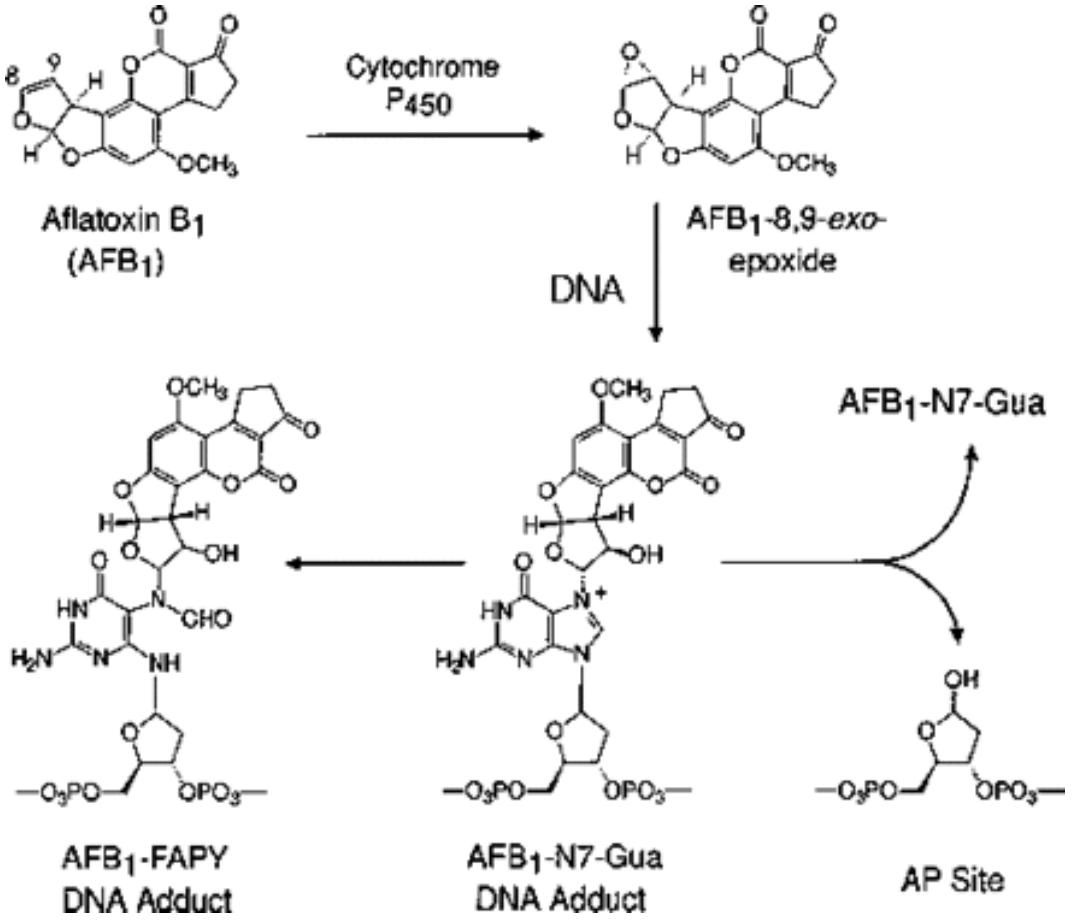


***N*^{3}-Mehtylcytosine** (C)
replication block

DNA Alkylation Example 1: Aflatoxin

- Produced by fungi (*Aspergillus sp.*) found in soil
- Dietary exposure: contamination of grains, seeds and nuts in high temperature and high humidity storage
- Liver carcinogen – amongst most potent liver toxicants
- Contributor to high incidences of liver cancer in China and West Africa

N7-Aflatoxin Alkylation



1. Metabolic activation

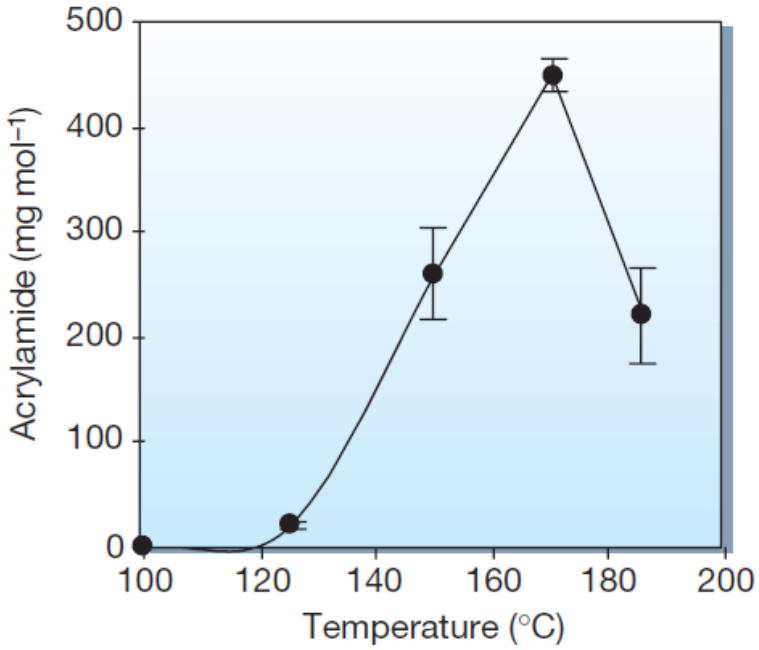
2. Alkylation of DNA
3. Two competing damage outcomes
   - Depurination (strongly promoted by alkylation)
   - Adduct Hydrolysis

Nucl. Acids Res. (1996) 24 (14): 2821-2828. doi: 10.1093/nar/24.14.2821

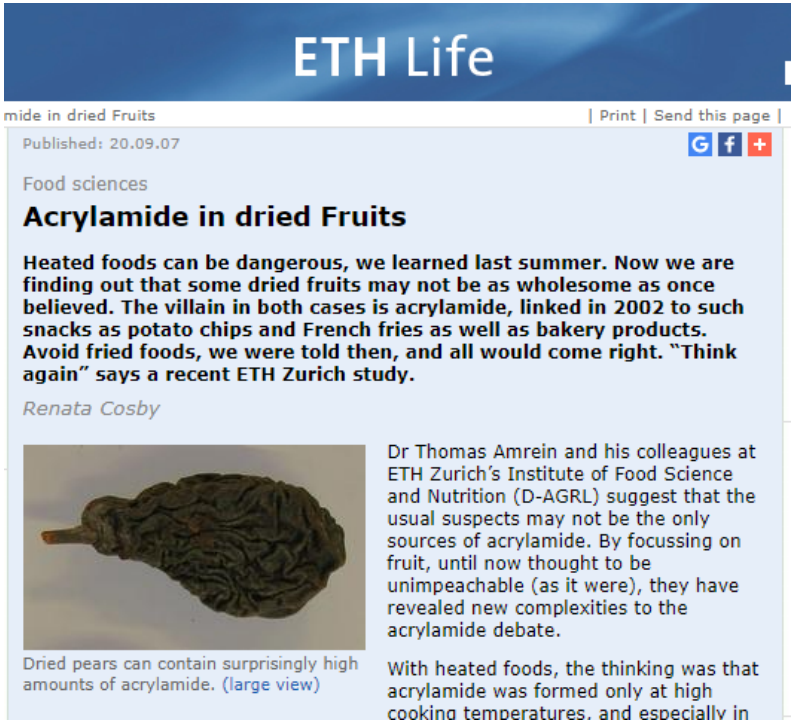
Example 2: Acrylamide

- Occupational exposure to acrylamide has been long known, but exposure of acrylamide by dietary exposures has been a focus in past ~15 years
- IARC Group 2A (Probable)

Formation of acrylamide from asparagine and glucose



Stadler, R. et al. Nature, 2002. 419, 448



ETH Life

mide in dried Fruits | Print | Send this page |

Published: 20.09.07

Food sciences

Acrylamide in dried Fruits

Heated foods can be dangerous, we learned last summer. Now we are finding out that some dried fruits may not be as wholesome as once believed. The villain in both cases is acrylamide, linked in 2002 to such snacks as potato chips and French fries as well as bakery products. Avoid fried foods, we were told then, and all would come right. "Think again" says a recent ETH Zurich study.

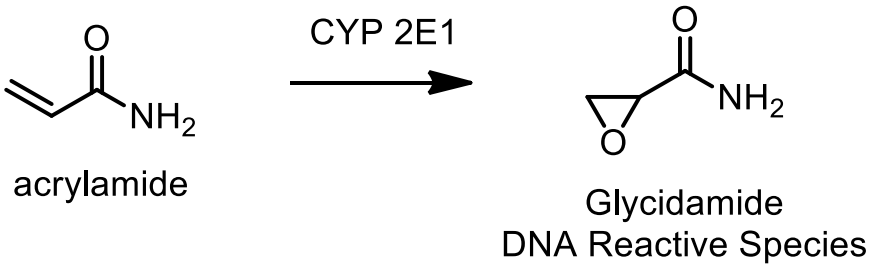
Renata Cosby

Dried pears can contain surprisingly high amounts of acrylamide. (large view)

Dr Thomas Amrein and his colleagues at ETH Zurich's Institute of Food Science and Nutrition (D-AGRL) suggest that the usual suspects may not be the only sources of acrylamide. By focussing on fruit, until now thought to be unimpeachable (as it were), they have revealed new complexities to the acrylamide debate.

With heated foods, the thinking was that acrylamide was formed only at high cooking temperatures, and especially in

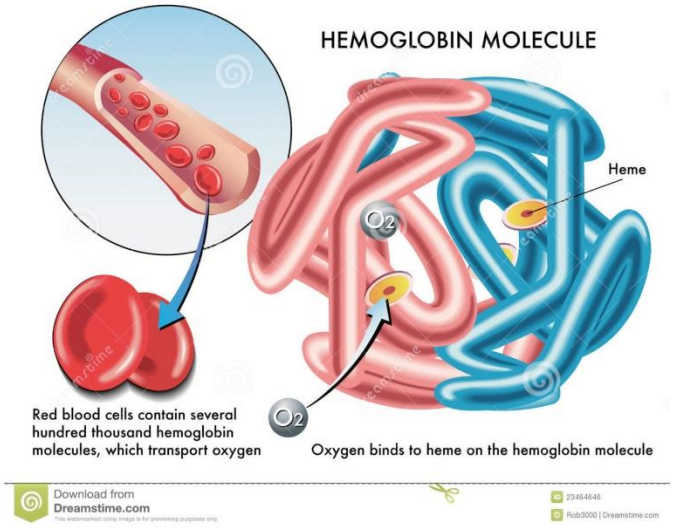
Bioactivation and DNA Alkylation by Acrylamide



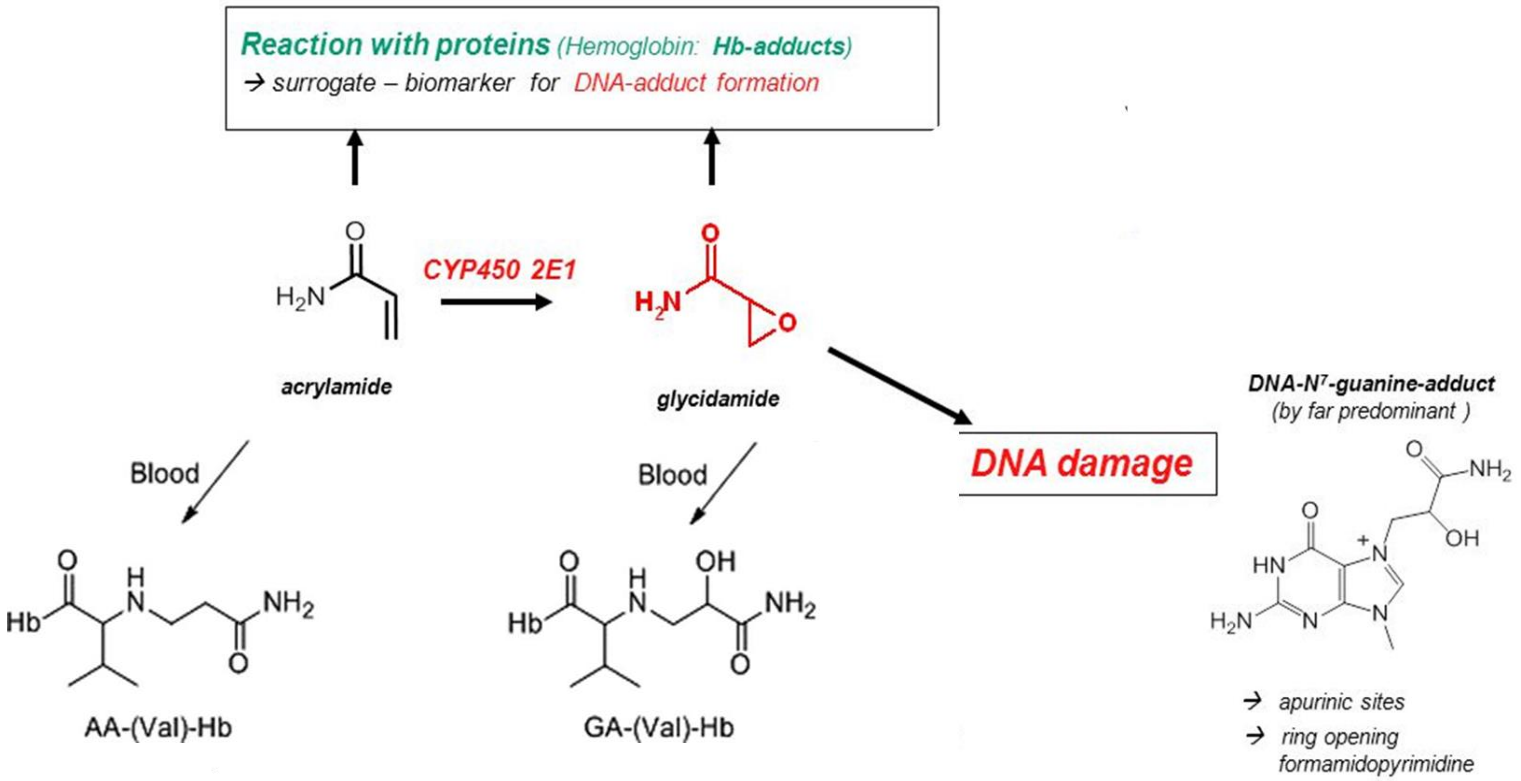
- Acrylamide is metabolically activated by P450 to form glycidamide (DNA reactive epoxide)
- Detoxification by GSH reaction (Mentimeter)
- DNA reacts at multiple positions and at both sides of the epoxide

Acrylamide Biomonitoring

- hemoglobin adducts (in blood) are markers of integrated acrylamide exposure over the preceding few months.
- levels increase with dietary intake
- smokers have adduct levels three to fourfold higher than non-smokers; most non-smokers less than about 100 pmol/gram hemoglobin.
- levels influenced by enzyme polymorphisms
- Younger children may have slightly higher levels possibly due to increased intake of acrylamide-containing foods relative to body size



Acrylamide Hb Adducts



Example of a protein adduct
(Biomarker for exposure)

Example 3: Polycyclic aromatic hydrocarbons (PAH)

Napthalaene
$C_{10}H_8$

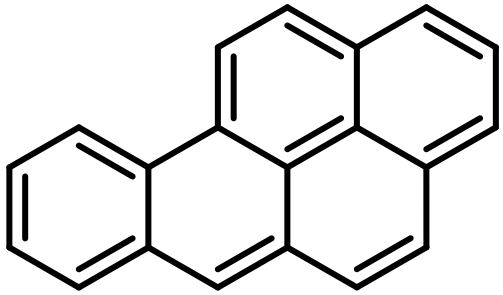
Chrysene
$C_{18}H_{12}$

Pyrene
$C_{16}H_{10}$

Coronene
$C_{24}H_{12}$

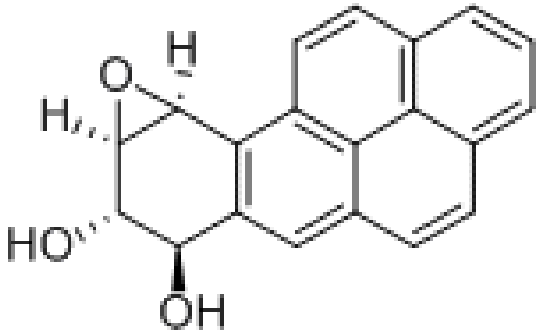
Ovalene
$C_{32}H_{14}$

How PAHs induce signature mutations: Genotoxic mechanism of carcinogenesis



Benzo[a]pyrene

Activation by P450



DNA Adduct

-alkylation of guanine

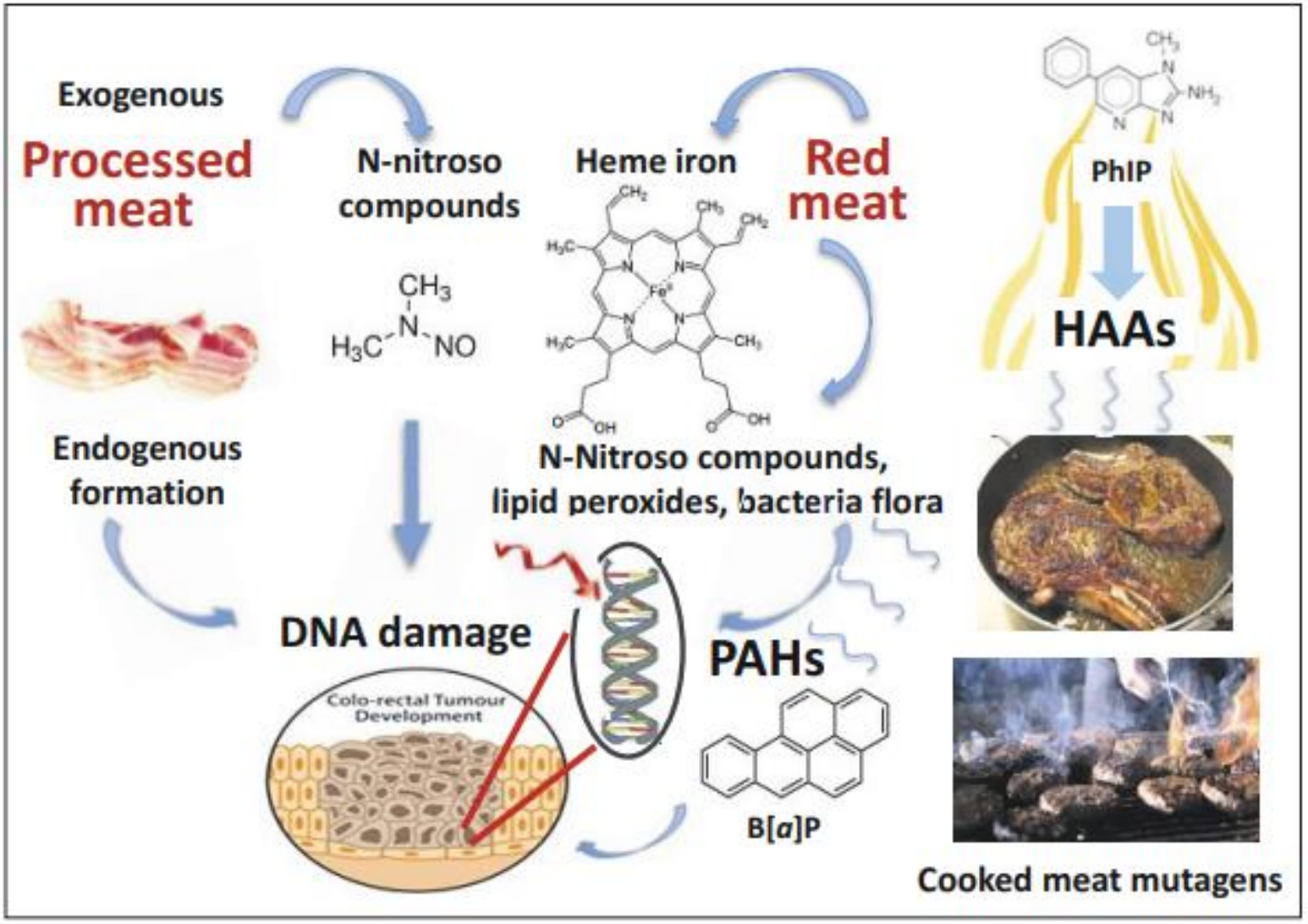
DNA Repair

Mutation Avoided

G to T Transversion Mutation

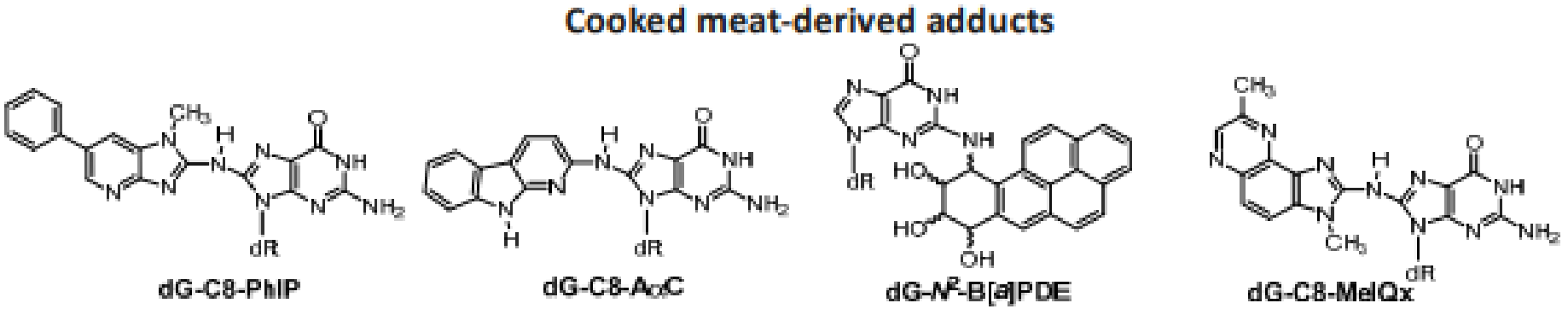
Translesion Synthesis

PAHs in cooked meat



Mechanistic Evidence for Red Meat and Processed Meat Intake and Cancer Risk: A Follow-up on the International Agency for Research on Cancer Evaluation of 2015

DNA adducts from PAHs



Mechanistic Evidence for Red Meat and Processed Meat Intake and Cancer Risk: A Follow-up on the International Agency for Research on Cancer Evaluation of 2015

DNA Adducts, Key Points

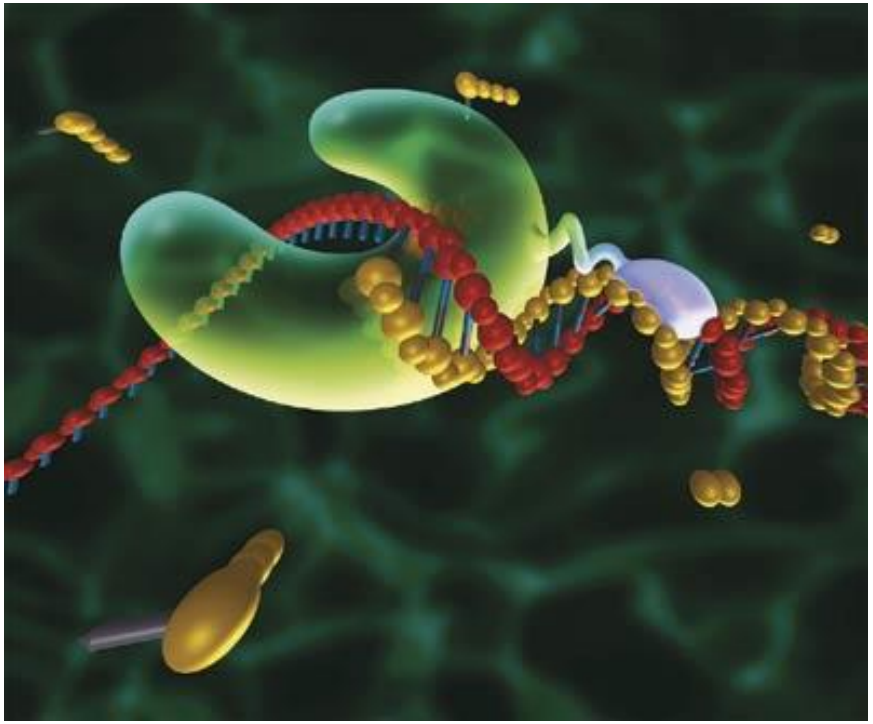
- Direct damage to DNA, changes chemical structure of DNA
- Key basis of genotoxic mechanism of carcinogenesis
- A DNA adduct is not a mutation, it is a precursor to a mutation when it is a substrate in DNA synthesis
- Formation of adducts is marker for exposure and risk, therefore efforts to identify structures, properties and levels

Lecture 2, Part 3

MUTAGENESIS (TRANSLESION DNA SYNTHESIS)

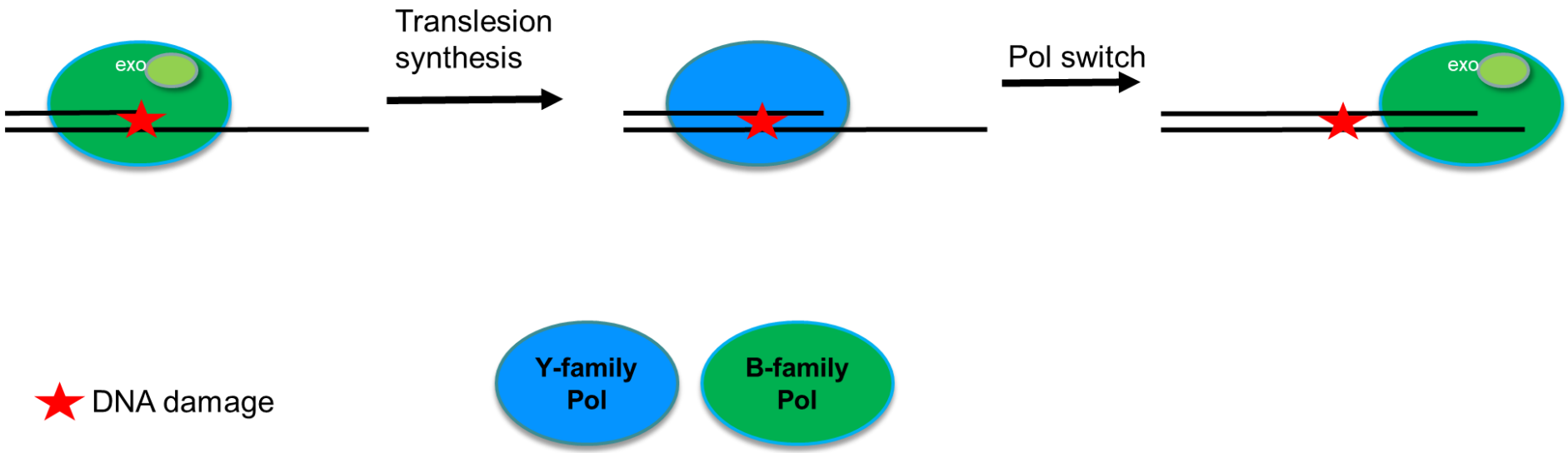
DNA Polymerases

- Role of replicative Pols
- TLS Pols characteristics
  - rates and fidelity
  - active site properties
  - proofreading
  - processivity



TLS: Translesion DNA Synthesis

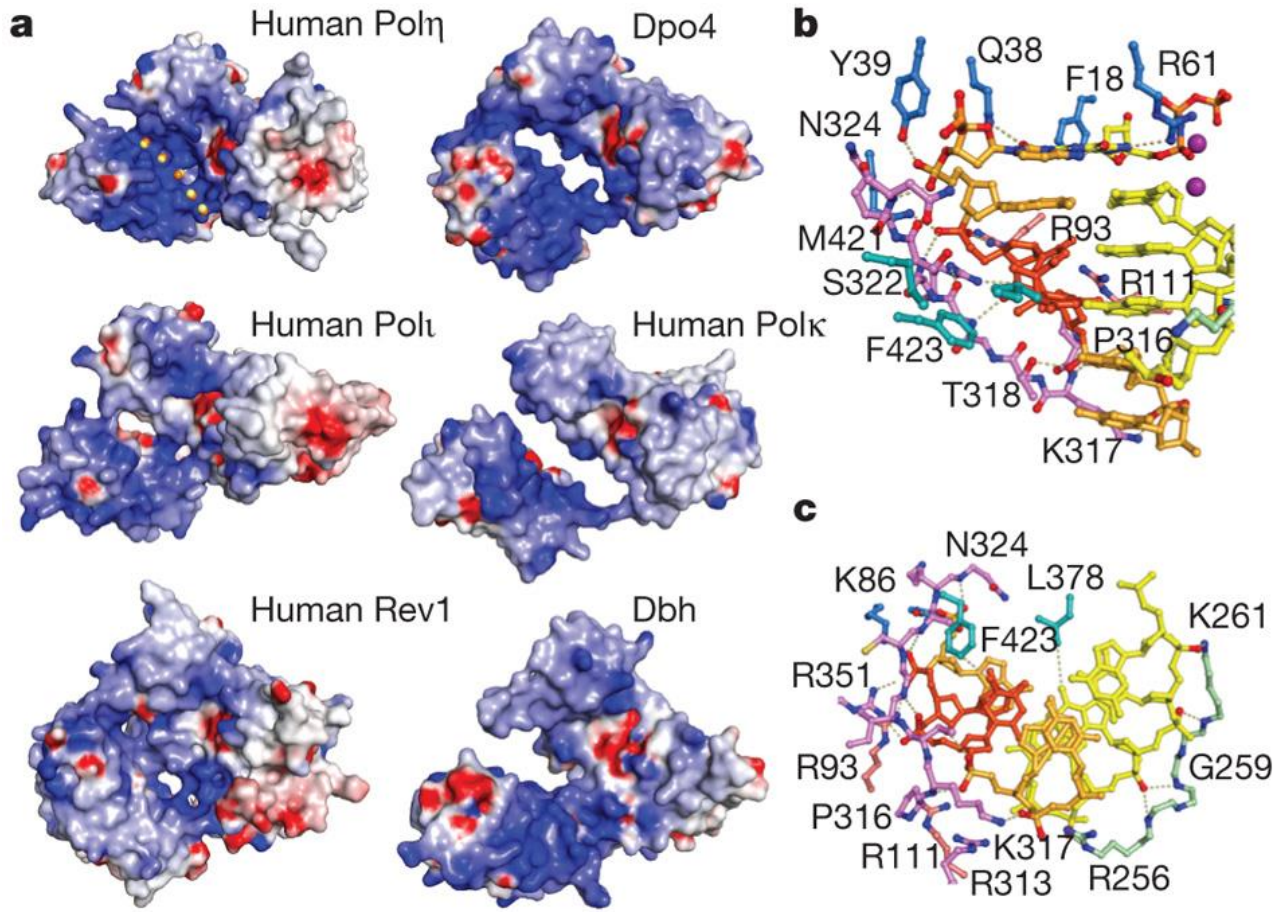
Y-family polymerases catalyze translesion DNA synthesis



DNA binding of Y-family DNA polymerases

Red (+)

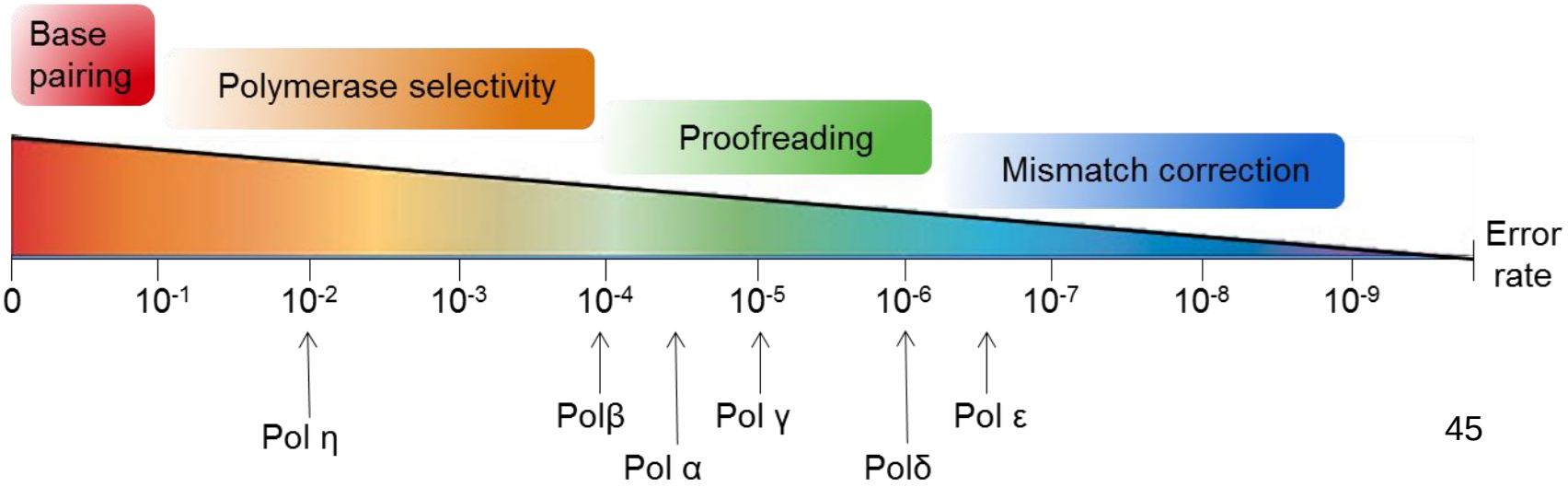
Blue (-)



C Biertümpfel *et al. Nature* **465**, 1044-1048 (2010) doi:10.1038/nature09196

Comparing Polymerases

Characteristic	B Family Polymerases (δ, ε)	Y Family Polymerases (η, ι, κ)
Error Rate	Low (< 10^{-10}/bp)	High (10^{-2} to 10^{-4})
Fidelity	High	Low
Proofreading	3’ exonuclease	None
Processivity	High	Low

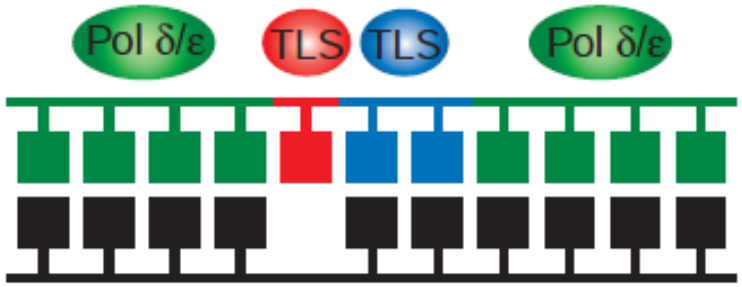


Polymerase Switching Models

- Basic DNA Pol Switch Model

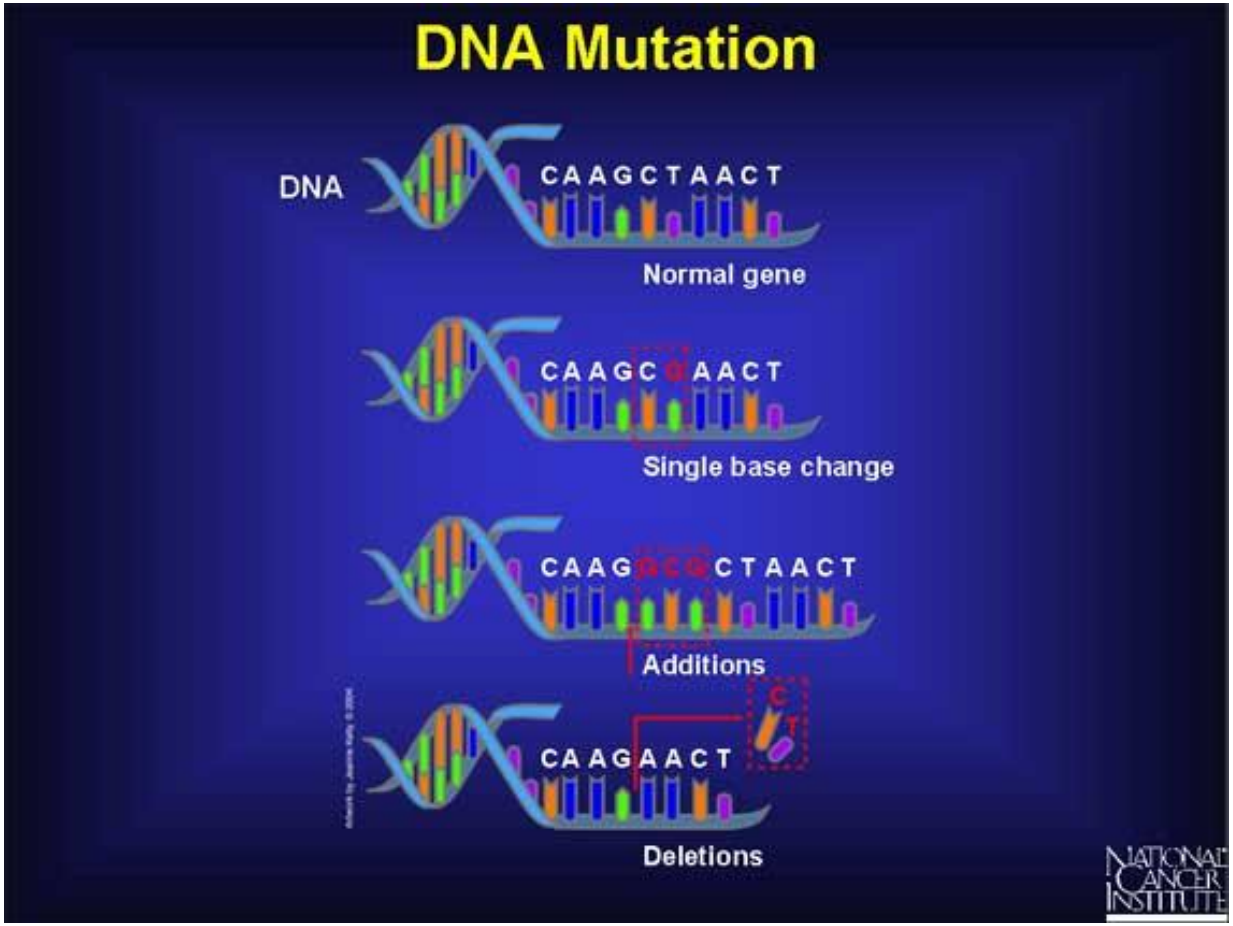
- 2 relevant mechanisms for TLS, depending on the lesion structure and active enzymes

One TLS polymerase (red) responsible for insertion and extension.



Two TLS polymerases (red and blue) responsible for insertion and extension.

Types of mutations induced by genotoxins



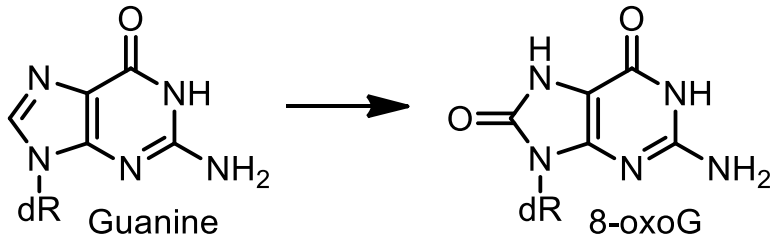
- Point/Single Base Change
  - transversion
  - transition
- Frame shift-causing
  - Deletion
  - Insertion/Addition

Outcomes of mutations

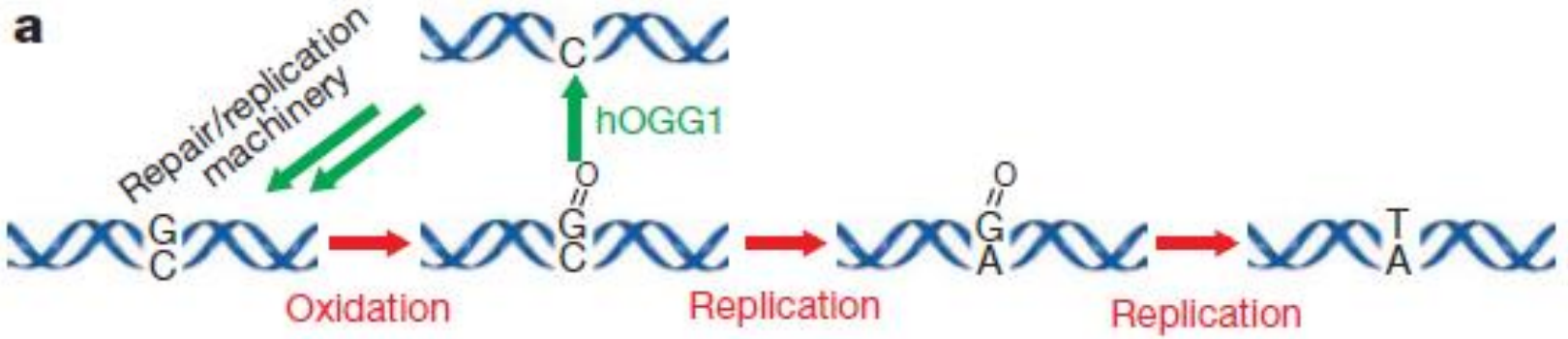
- Translation into mutant proteins
- Lethality
- Mutant can be recognized and repaired
- Cells expressing mutant proteins can be recognized and eliminated
- Mutant proteins can impart cancer phenotype

Mutagenesis Example: Oxidation-Induced Mutagenesis

- Polymerase-mediated DNA replication of 8-oxoG often incorporates an A
- This mismatch (8oxoG:A) is not proofread efficiently
- The poor proofreading can be attributed to the geometry of 8-oxo-G:A, which is similar to that of the correct base pair

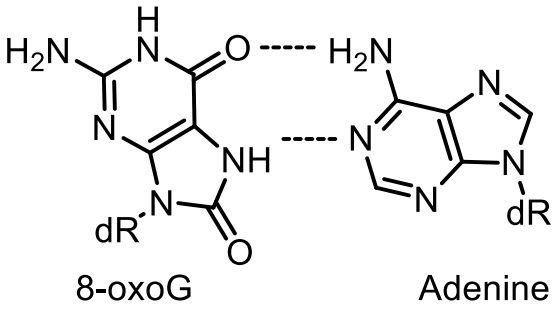


Replication of the Lesion 8oxoG



8oxoG causes G -> T transversions

8oxoG-A base pair is geometrically Similar to the natural G-C base pair



Bruner, S. *et al.* Nature. 2000. 403, 859-866

Determinants of Replication Fidelity and Mutation Rates

- Biochemical Factors related to the polymerase enzyme
  - Expression levels
  - Regulation
  - Kinetic behavior/accuracy
- Chemical Factors
  - Structure/size of the modification

    (this also dictates which polymerase is active)
  - Watson-Crick H-bonding
  - Base Stacking Interactions with neighboring bases as well as aromatic residues on the enzyme
  - A-Rule (DNA polymerases insert Adenine opposite abasic sites)
- Elimination of damage by Repair!

Lecture 2, Part 4

DNA REPAIR

Why is DNA repair important and why do we want to understand it?

- Mitigate damaging effects of endogenous DNA damage that is formed at high rates
  - oxidative lesions
  - Abasic sites
- Protect against carcinogenesis from xenobiotic agents
- Is a significant source of drug resistance in cancer chemotherapy

2015 Nobel Prize in Chemistry

Tomas Lindahl (Swedish), Francis Crick Institute, UK
Paul Modrich (American), Duke University, USA
Aziz Sancar (Turkish), Univ North Carolina, Chapel Hill, USA

“mechanistic studies of DNA repair"

http://www.nobelprize.org/nobel_prizes/chemistry/

NOBEL PRIZE IN CHEMISTRY 2015

The Nobel Prize in Chemistry 2015 was awarded to **Tomas Lindahl**, **Paul Modrich**, and **Aziz Sancar** for having mapped how cells repair damaged DNA.

DNA DAMAGE

BASES: A PAIRS WITH T C PAIRS WITH G

DNA damage occurs regularly, due to UV radiation, carcinogenic substances, & copying errors. The prize is for the discovery of the mechanisms that repair this damage.

BASE EXCISION REPAIR

1. C loses amino group to form U. U can't pair with G.
2. Enzymes remove U and its section of the DNA strand.
3. The correct base is inserted and the strand is sealed.

DNA is an unstable molecule. Lindahl showed that base excision repair prevents its decay. Without this mechanism, development of life would have been impossible.

NUCLEOTIDE EXCISION REPAIR

1. UV radiation can cause two Ts to bind to each other.
2. Enzyme cuts a 12 nucleotide strand, removing damage.
3. The resulting gap in the DNA is filled and then sealed.

Sancar explained how DNA is repaired after damage from UV and mutagenic substances. People with defects in this repair system are at higher risk of developing cancer.

MISMATCH REPAIR

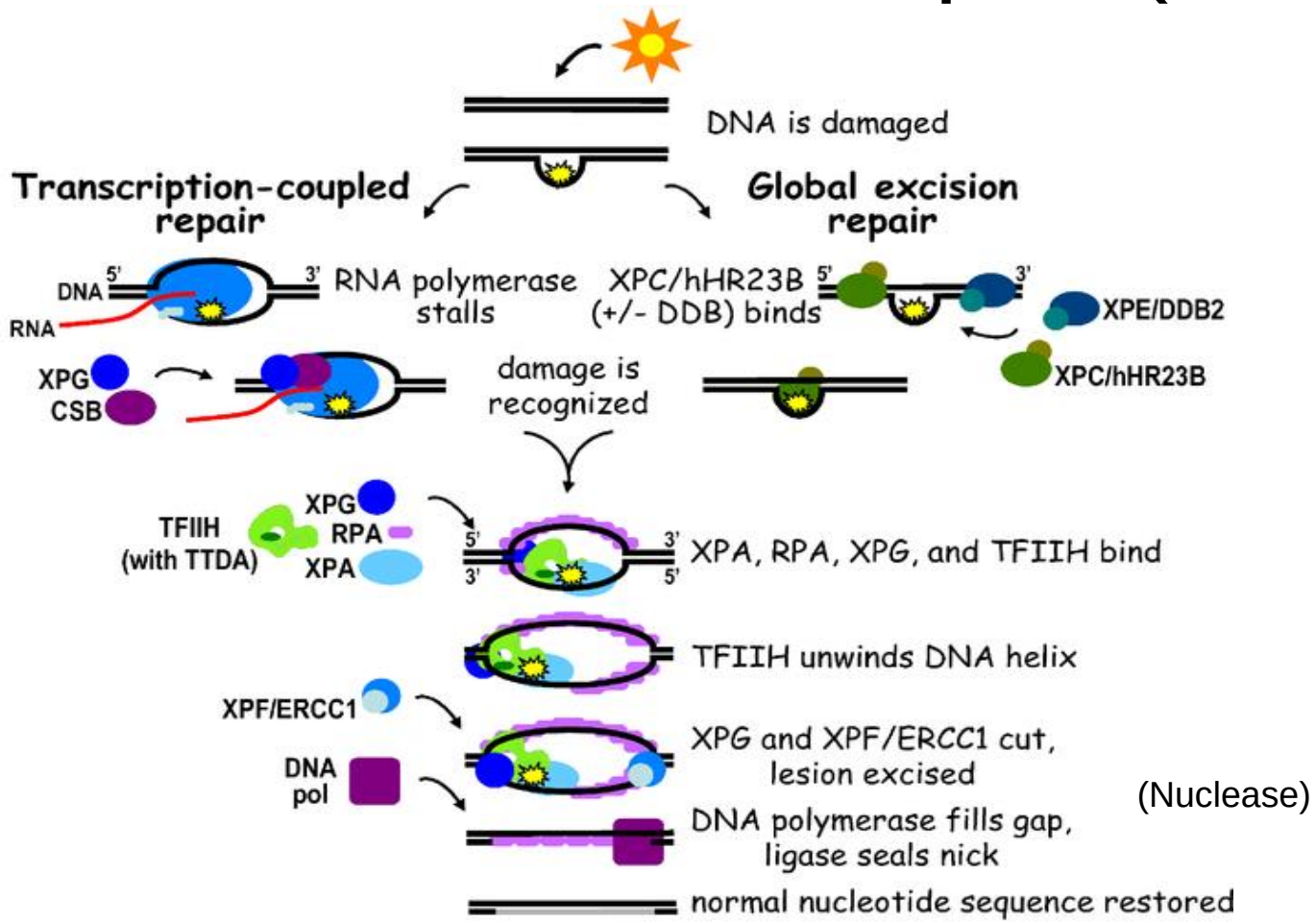
1. Sometimes the nucleotides in copied DNA don't match.
2. Enzymes remove a section containing the faulty nucleotide.
3. The resulting gap in the DNA is filled and then sealed.

Modrich showed how errors produced when cells divide and DNA is replicated are repaired. This reduces the error rate of DNA replication by a factor of 1000.

DNA Repair Pathways

1. Nucleotide excision repair
2. Base excision repair
3. Mismatch repair
4. Homologous recombination
5. Non-homologous end-joining
6. Dealkylation (Direct reversion)

1. Nucleotide excision repair (NER)

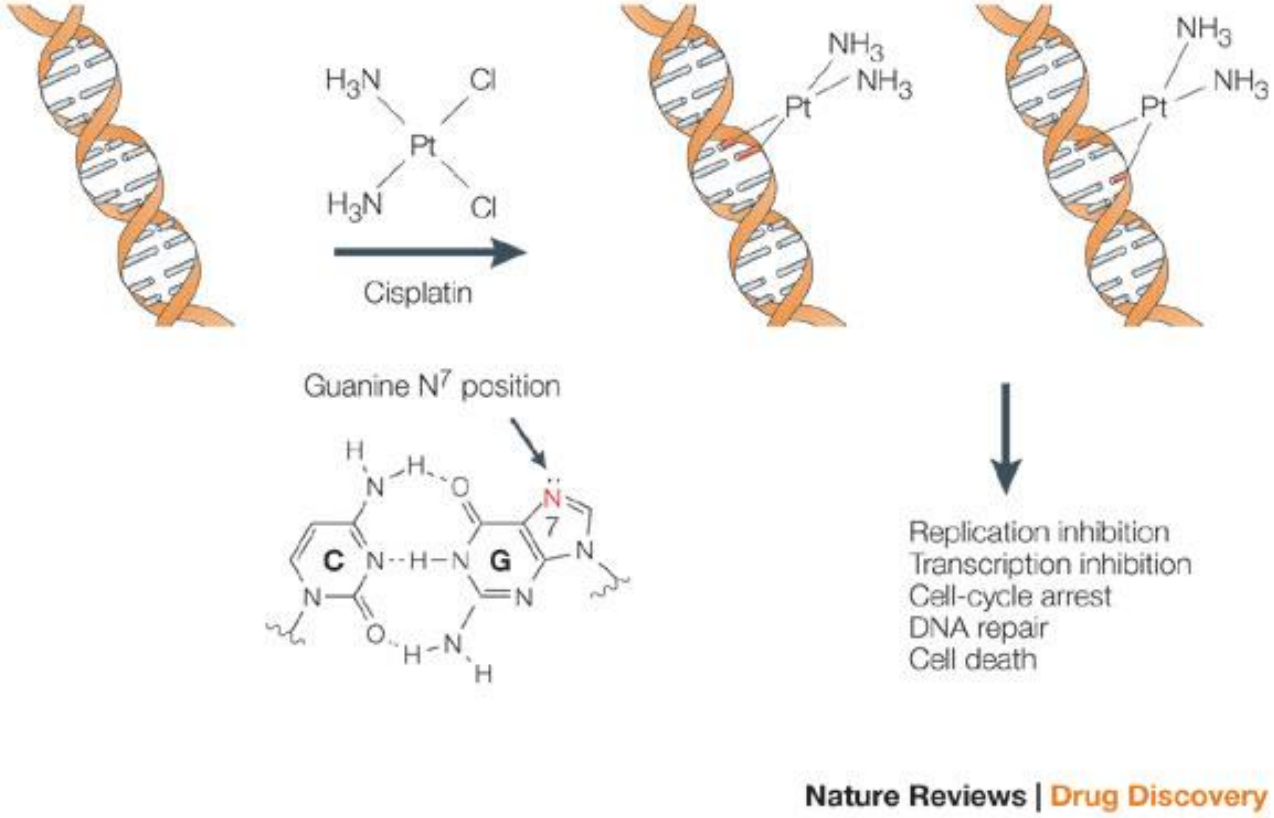


(Nuclease)

1. Recognition; 2. Assembly of multi-protein complex for remodeling and cutting; 3. removal of short single-stranded DNA segment containing lesion; 4. DNA synthesis (polymerase); 5. ligation (ligase)

NER substrates

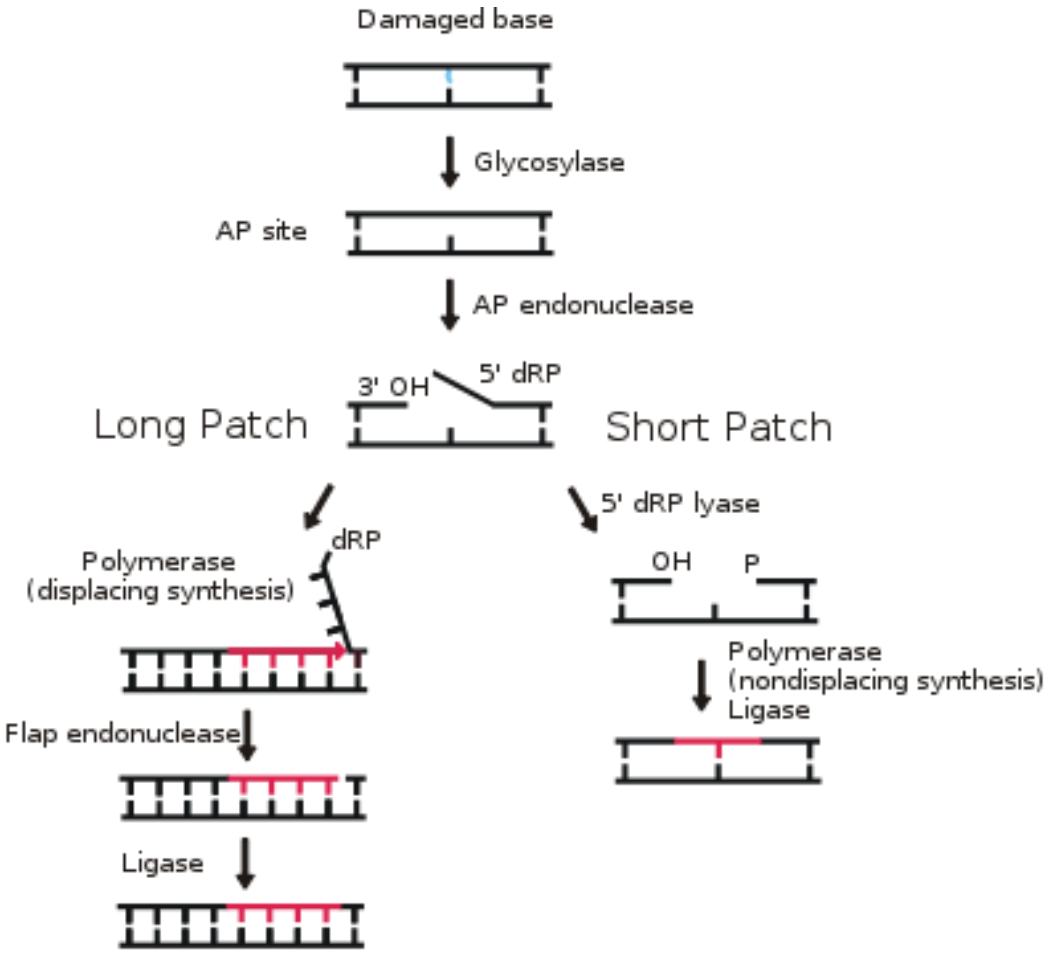
- bulky, helix-distorting DNA damage
  - thymine dimers and 6,4-photoproducts (UV exposure).
  - Chemotherapy-induced DNA crosslinks (Pt drugs as shown below)



http://www.nature.com/nrd/journal/v4/n4/fig_tab/nrd1691_F3.html

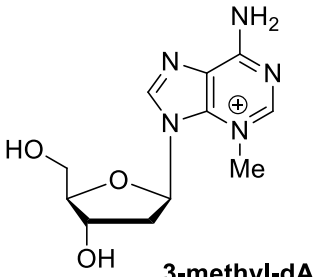
2. Base excision repair (BER)

- small, non-helix-distorting base adducts
- Initiation: DNA <u>glycosylases</u>
  - recognize damage
  - remove altered bases
  - form AP sites
- AP sites cleaved by AP <u>endonuclease</u>
- New DNA synthesized by polymerase
  - In short-patch single nucleotide is replaced
  - In long-pach 2-10 nucleotides are synthesized and flap endonuclease trims displaced strand
- Strand sealed by <u>ligase</u>

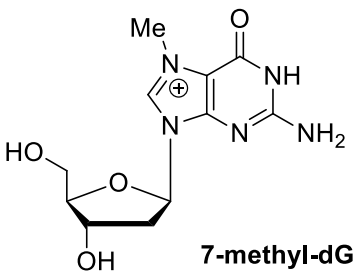


BER substrates

- Alkylated bases:
  - 3-methyladenine
  - 7-methylguanine



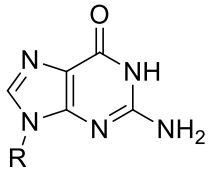
3-methyl-dA



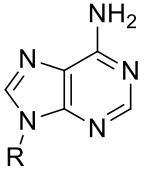
7-methyl-dG

- Oxidized bases:
  - 8-oxoguanine

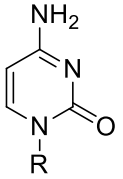
- Deaminated bases:
  - xanthine
    - deamination of G
  - hypoxanthine
    - deamination of A
  - uracil
    - deamination of C



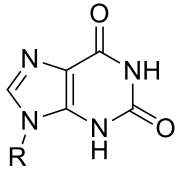
guanine



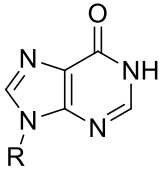
adenine



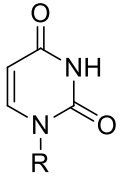
cytosine



xanthine



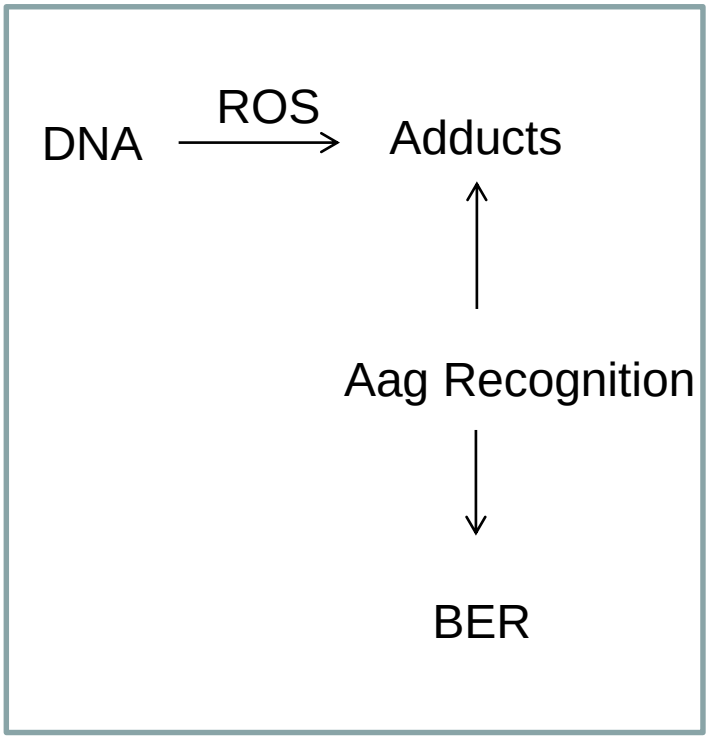
hypoxanthine



uracil

DNA damage induced by chronic inflammation contributes to colon carcinogenesis

- chronic inflammation increases cancer risk
- ROS induce DNA damage recognized by alkyladenine DNA glycosylase (Aag)
- Aag recognition of adduct initiates base excision repair

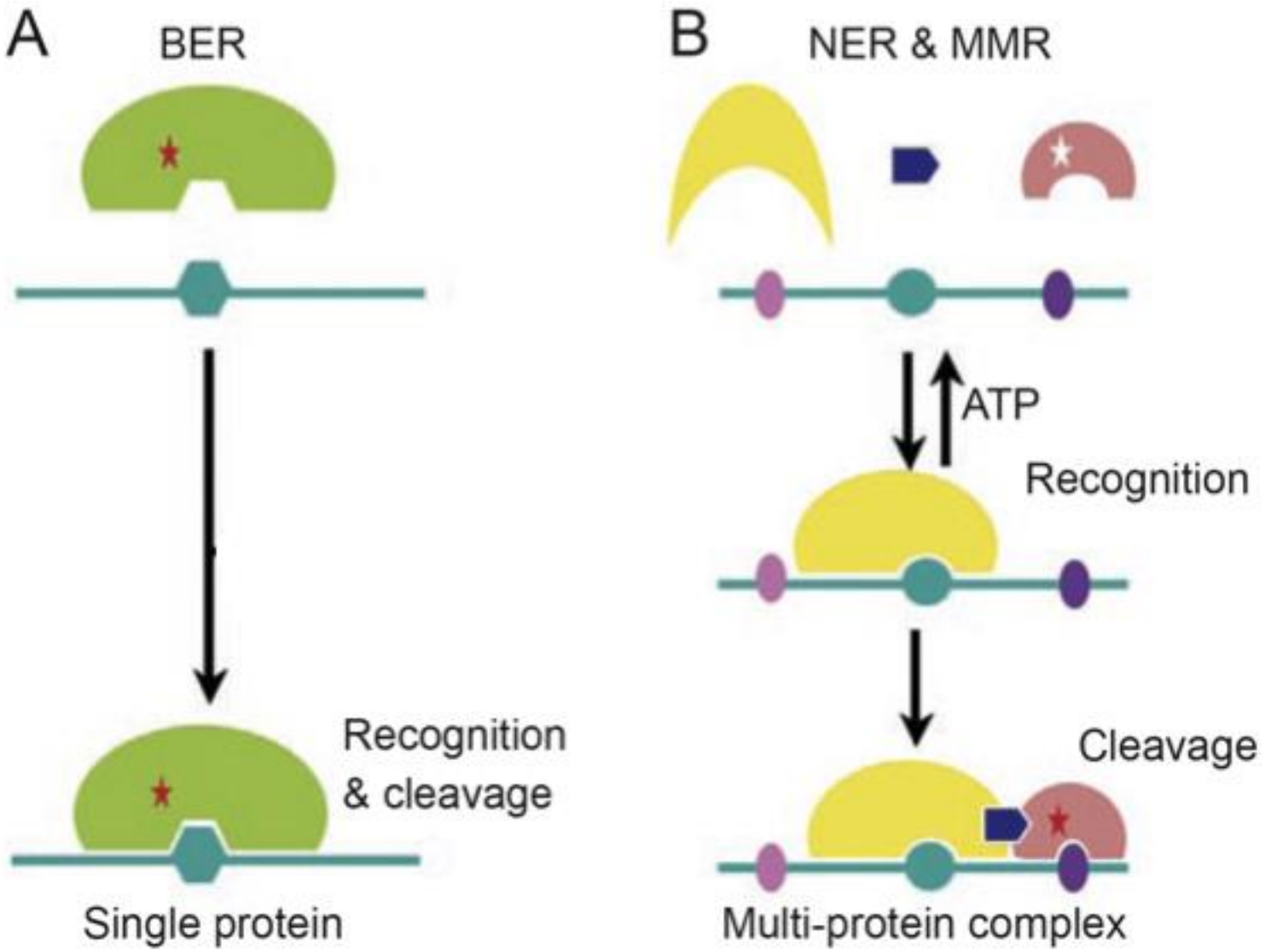


J Clin Invest. 2008 July 1; 118(7): 2516–2525. doi: 10.1172/JCI35073

Importance of BER in protection against colon carcinogenesis

- Impacts of Aag-mediated DNA repair (+Aag mice)
  - prevents colonic epithelial damage
  - reduces the severity of chemical–induced colon tumorigenesis
- Accumulation of DNA adducts in Aag-deficient mice following stimulation of colonic inflammation

STRATEGIES USED FOR DAMAGE RECOGNITION



Yang, Cell Res. *18*, 184-197 (2008)

Study Tip: What to know for repair pathways

- Similarities and differences in processes for recognition, removal, replacement synthesis, ligation
- Understand basic process and relevant enzyme types Example:
  - ➢ in BER, small alkyl adduct is recognized and excised by a glycosylase
  - ❑ In BER, 3-methyl adenine is recognized and excised by alkyladenine DNA glycosylase (Aag)
- Characteristics of damage – what pathway is relevant?

3. Mismatch repair

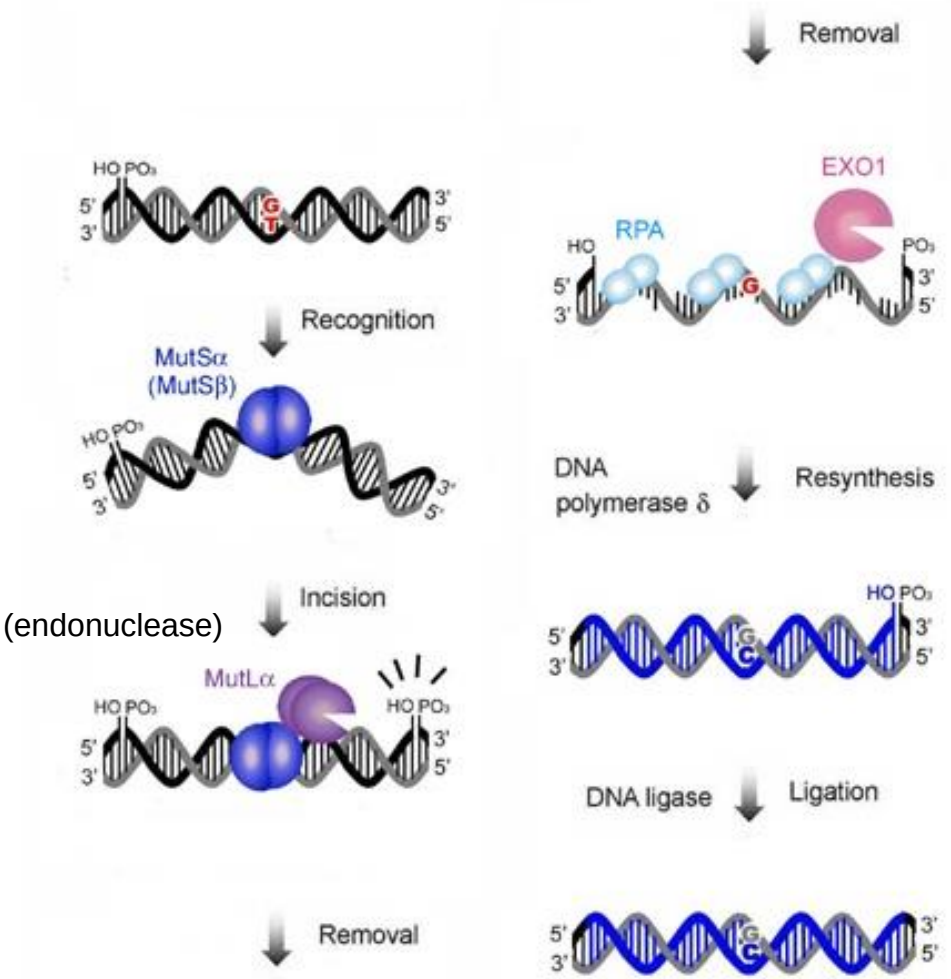
- *DNA mismatch repair* repairs mis-incorporated bases during DNA replication.

- MutS recognizes and binds mismatch
- MutL makes incision, DNA contains nicks not yet sealed by DNA ligase

- Patch is removed (RPA, replication protein A; EXO1, exonuclease 1)

- DNA synthesis (polymerase) and ligation (ligase)

- Hereditary nonpolyposis colorectal cancers attributed to mutations in the genes encoding MSH2 and MLH1 respectively
  - MSH2 and MLH1 = tumour suppressor genes.



DNA Repair Pathways

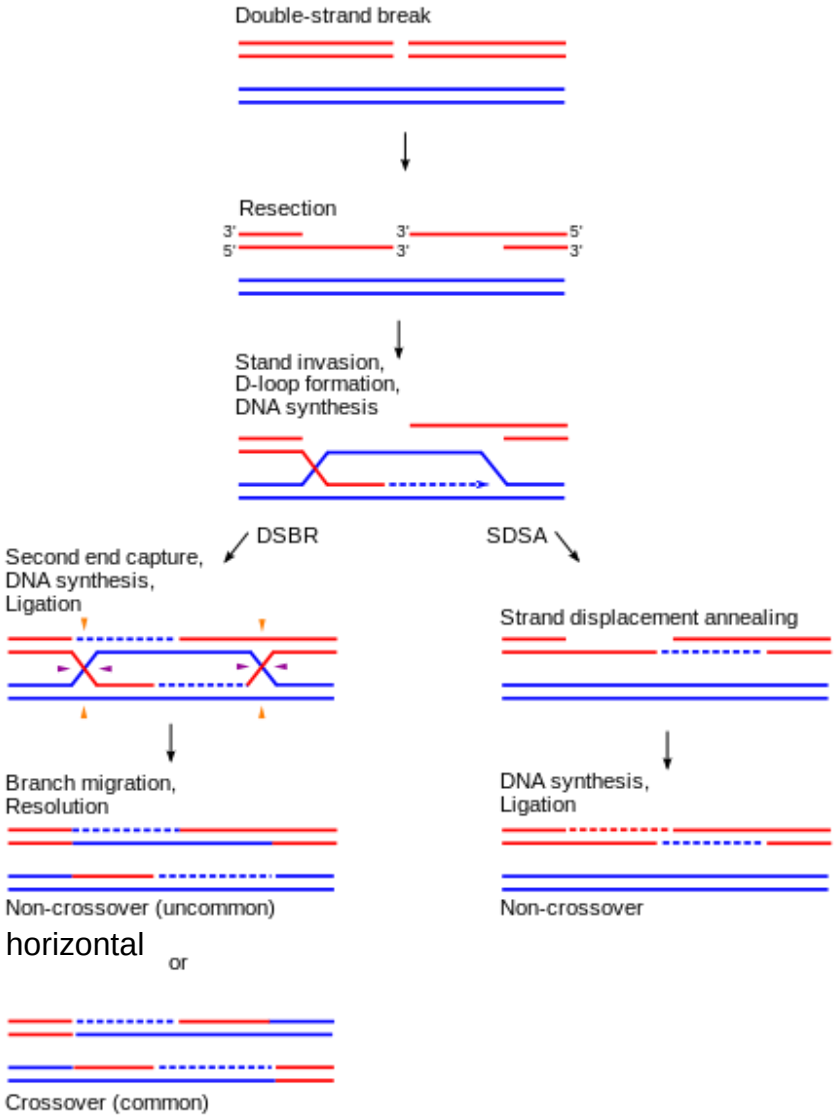
- ✓ Nucleotide excision repair
- ✓ Base excision repair
- ✓ Mismatch repair
4. Homologous recombination
5. Non-homologous end-joining
6. Dealkylation (Direct reversion)

4. Homologous Recombination

- After double-strand break
- sections of DNA around the 5' ends of the break are cut away in a process called *resection*.
- In the *strand invasion* step that follows, an overhanging 3' end of the broken DNA molecule then "invades" a similar or identical DNA molecule that is not broken (sister chromatid in mitosis).

- After strand invasion:
  - DSBR (double-strand break repair) or
  - SDSA (synthesis-dependent strand annealing)

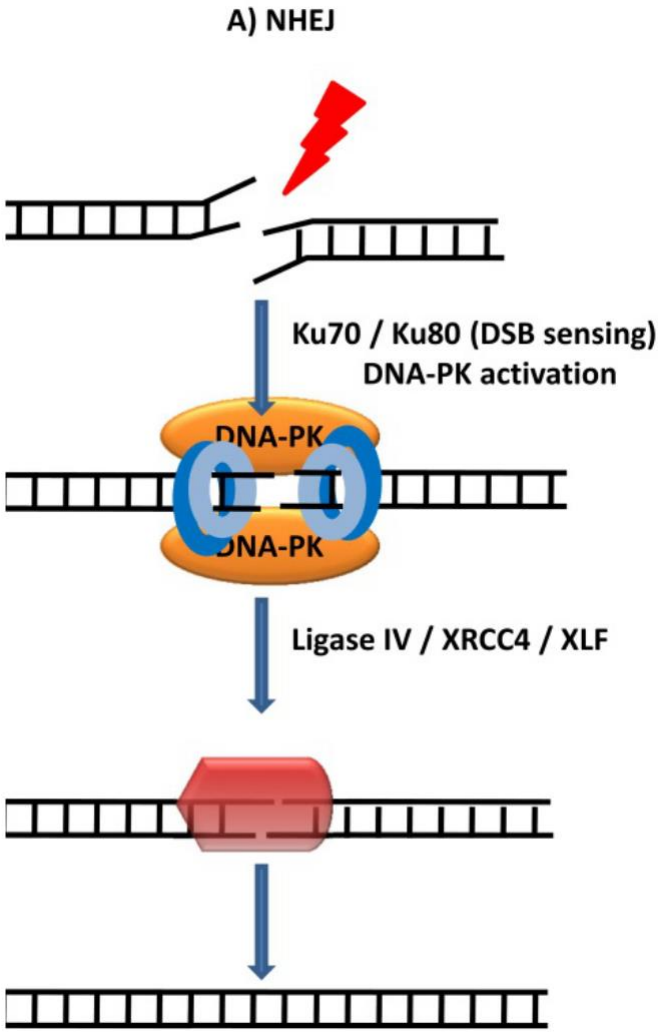
VIDEO ON HR REPAIR



http://en.wikipedia.org/wiki/File:HR_schematic_diagram.svg

5. Non-homologous end-joining (NHEJ)

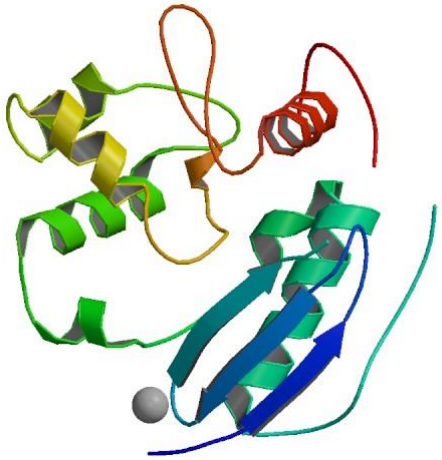
- Recognition: Ku70/Ku80 encircles duplex DNA at DSB
- Ku70/Ku80 stabilizes/structurally aligns the two DNA ends and recruits DNA-Protein Kinase (PK).
- DNA-PK phosphorylates and activates the NHEJ effector complex (ligase IV/XRC44/XLF) that ligates broken DNA.



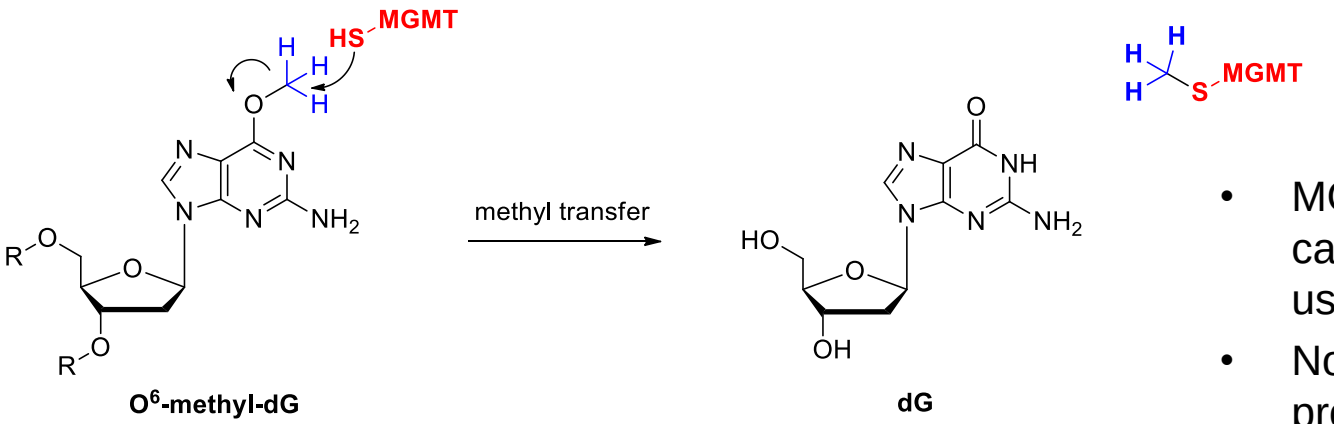
-NHEJ more common than HR
(NHEJ fast 30 min, HR slow 7 hrs)
-But more mutagenic!

http://www.intechopen.com/books/protein-phosphorylation-in-human-health/signalling-dna-damage

6. Direct reversion/Dealkylation repair



O-6-methylguanine methyltransferase (MGMT)



O^6-methyl-dG

dG

- MGMT is consumed; can no longer be used.
- Non-enzymatic process

MGMT and cancer

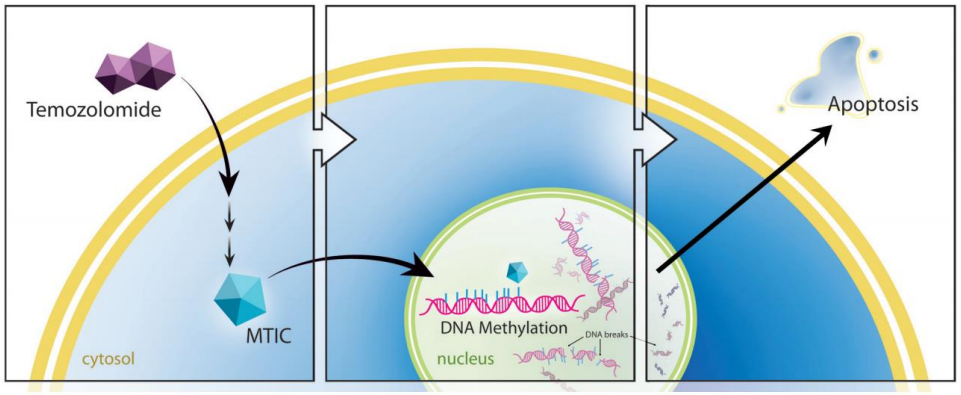


Fig 1. Schematic illustration of the proposed mechanism of temozolomide. Temozolomide is converted intracellularly into MTIC, which methylates DNA. Cellular repair mechanisms cannot adjust, resulting in DNA nicks and ultimately apoptosis.

-Temzolomide is an alkylating cancer drug

-MGMT inhibitors sensitize cancer cells to temzolomide therapy (targeting DNA repair proteins in cancer therapy)

-438 known polymorphisms of MGMT:

-*Gly160Arg.* Here, Gly160 residue lies nearby the Cys145 active site (rare variant found in less than 1% of Caucasians, but it is expressed in approximately 15% of Japanese).

-This polymorphism has generated interest due to its strong resistance to the MGMT inhibitor O^6-BG. Patients with this MGMT polymorphsims are not good candidates for O^6-BG therapy combined with alkylating agent treatment.

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DNA Repair Overview