Biological,chemical and physical agents leading to genetic and epigenetic modification, and mechanisms of action

MED 213

The Genetic Bases of Cancer

Oncogenes
Tumor suppressor genes
Repair genes

Biological,chemical and physical agents leading to genetic and epigenetic modification, and mechanisms of action

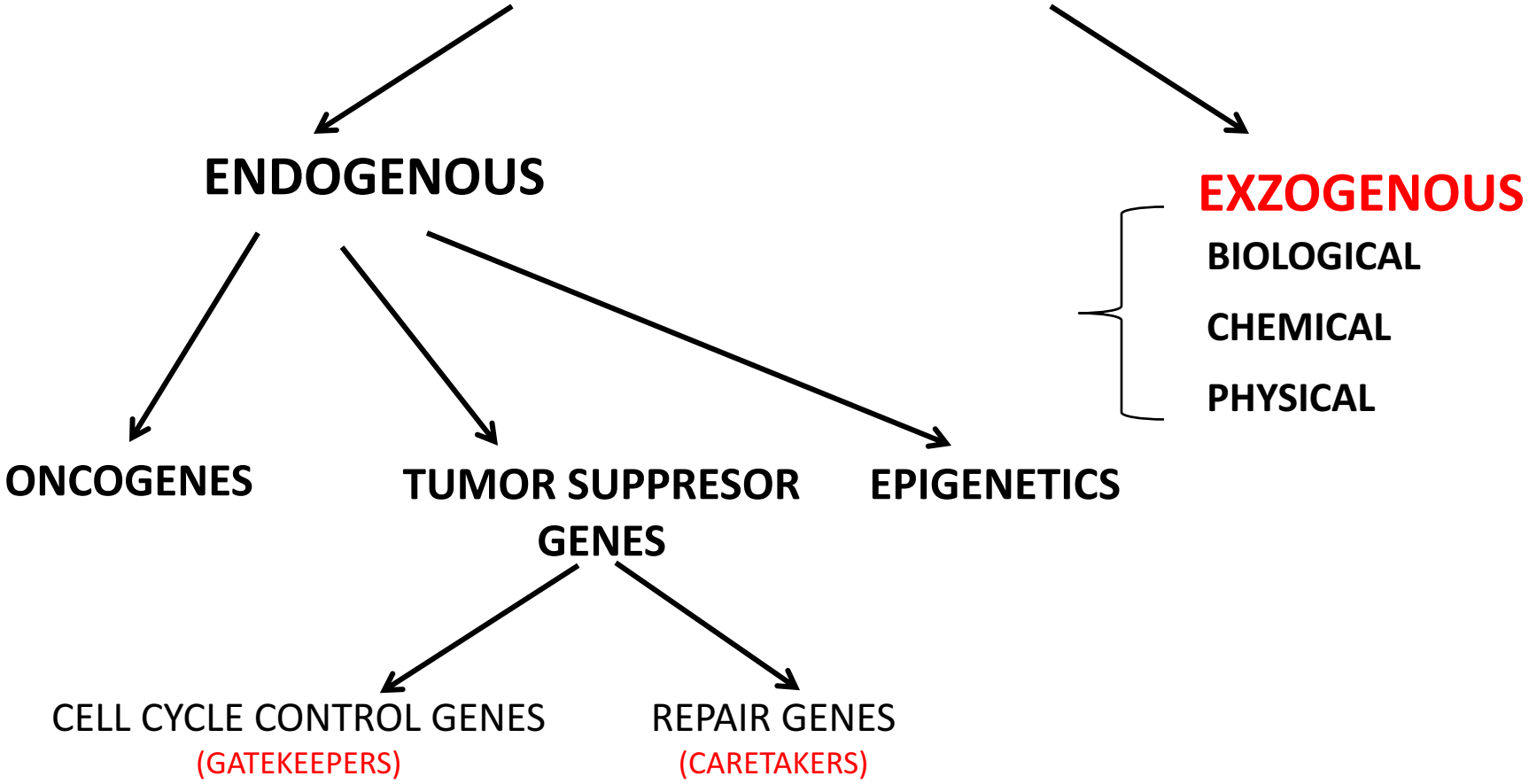
Genetic mechanisms in Familial vs Sporadic Cancers

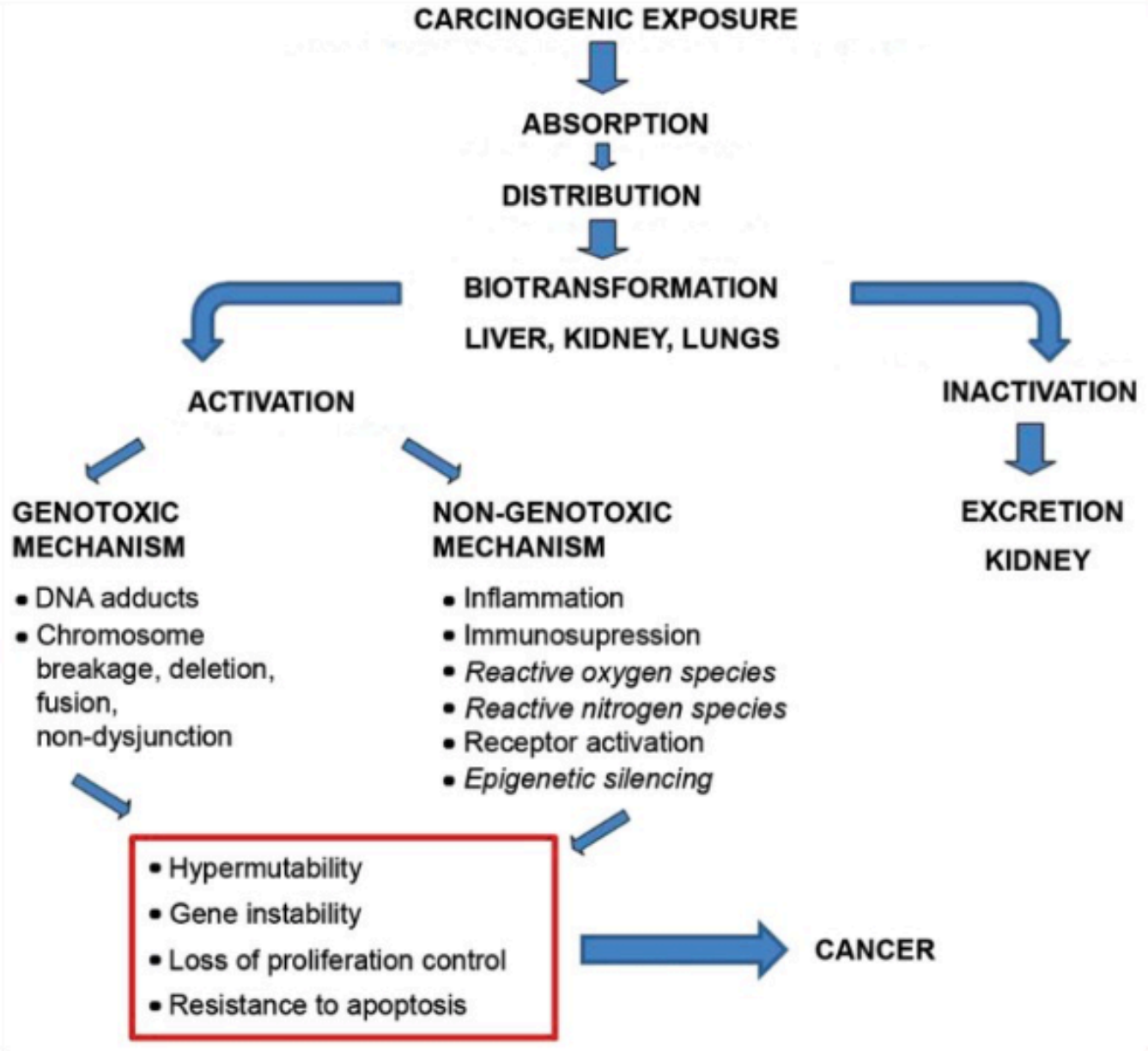
Pathways in Carcinogenesis

Epigenetics and Cancer

Molecular targets for Cancer Therapy

GENETIC MODIFICATIONS LEADING TO CARCINOGENESIS




CARCINOGENIC EXPOSURE
ABSORPTION
DISTRIBUTION
BIOTRANSFORMATION
LIVER, KIDNEY, LUNGS
ACTIVATION
INACTIVATION
GENOTOXIC MECHANISM
• DNA adducts
• Chromosome breakage, deletion, fusion, non-dysjunction
NON-GENOTOXIC MECHANISM
• Inflammation
• Immunosupression
• Reactive oxygen species
• Reactive nitrogen species
• Receptor activation
• Epigenetic silencing
EXCRETION
KIDNEY
• Hypermutability
• Gene instability
• Loss of proliferation control
• Resistance to apoptosis
CANCER

Aflatoxin-B1

- Aspergillus flavus's mycotoxin

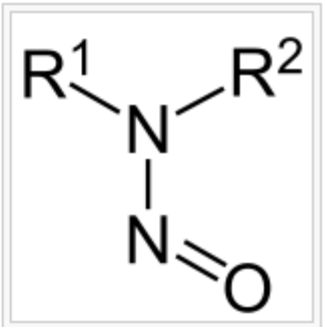
Metabolic conversion to exzo-8,9 epoxy compounds

Directly effects G bases

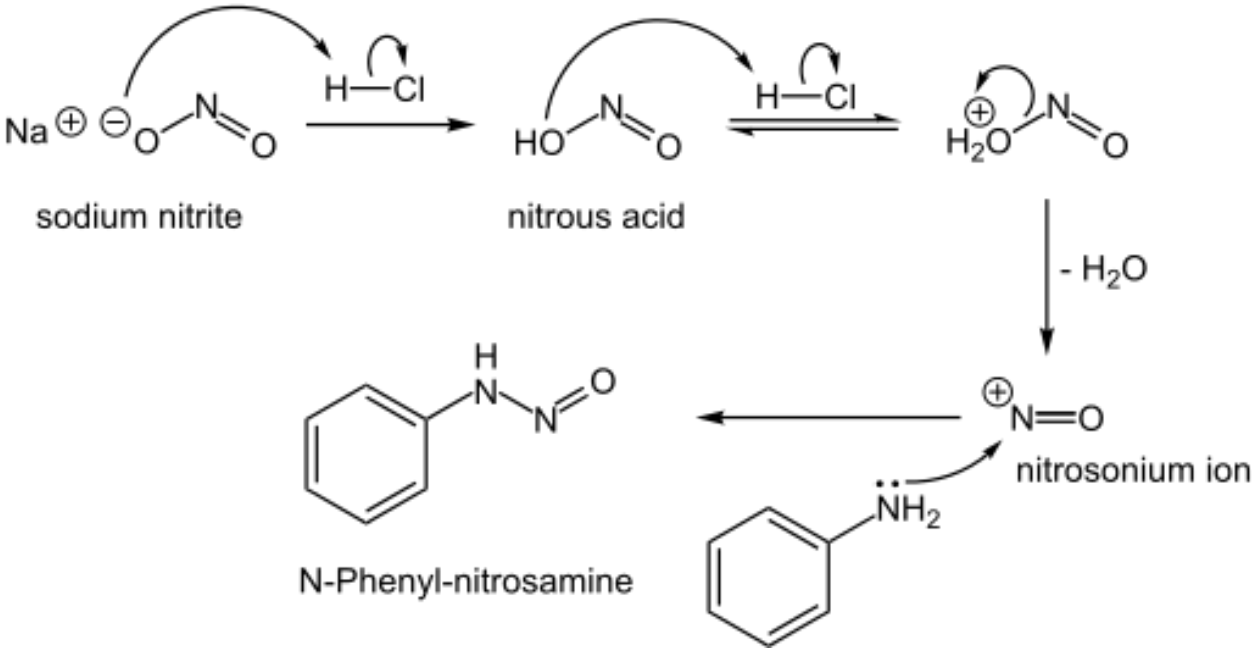
TP53: at 249th base position transversion to G>T

>50 % of tumors that arise in areas with high levels of environmental AFB1, a G→T transversion changes codon 249 of TP53 from AGG (encoding arginine, a basic amino acid) to AGT (encoding serine, a small nucleophilic amino acid).

N-nitrosamines



- Tobaco / Processed food / Red meet / Meet exposed to high tempratures
- Transversion : TGT→TGG, Insersion :CTG →CT**T**G, Delesyon:CTG → CG



International Agency for Research on Cancer

World Health Organization

PRESS RELEASE
N° 240

26 October 2015

IARC Monographs evaluate consumption of red meat and processed meat

Lyon, France, 26 October 2015 – The International Agency for Research on Cancer (IARC), the cancer agency of the World Health Organization, has evaluated the carcinogenicity of the consumption of red meat and processed meat.

Red meat

After thoroughly reviewing the accumulated scientific literature, a Working Group of 22 experts from 10 countries convened by the IARC Monographs Programme classified the consumption of red meat as *probably carcinogenic to humans* (Group 2A), based on *limited evidence* that the consumption of red meat causes cancer in humans and *strong* mechanistic evidence supporting a carcinogenic effect.

This association was observed mainly for colorectal cancer, but associations were also seen for pancreatic cancer and prostate cancer.

Processed meat

Processed meat was classified as *carcinogenic to humans* (Group 1), based on *sufficient evidence* in humans that the consumption of processed meat causes colorectal cancer.

Meat consumption and its effects

The consumption of meat varies greatly between countries, with from a few percent up to 100% of people eating red meat, depending on the country, and somewhat lower proportions eating processed meat.

The experts concluded that each 50 gram portion of processed meat eaten daily increases the risk of colorectal cancer by 18%.

“For an individual, the risk of developing colorectal cancer because of their consumption of processed meat remains small, but this risk increases with the amount of meat consumed,” says Dr Kurt Straif, Head of the IARC Monographs Programme. “In view of the large number of people who consume processed meat, the global impact on cancer incidence is of public health importance.”

The IARC Working Group considered more than 800 studies that investigated associations of more than a dozen types of cancer with the consumption of red meat or processed meat in many countries and populations with diverse diets. The most influential evidence came from large prospective cohort studies conducted over the past 20 years.

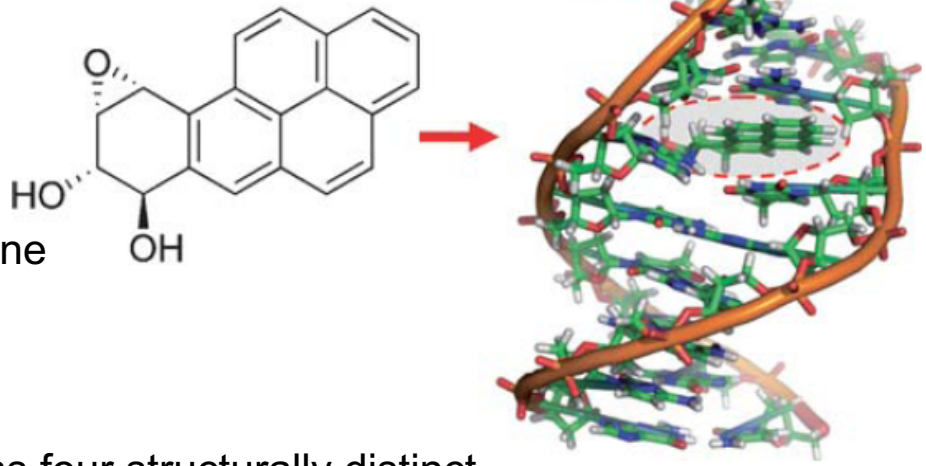
Public health

"These findings further support current public health recommendations to limit intake of meat," says Dr

Policyclic aromatic hydrocarbons (tobaco smoke)

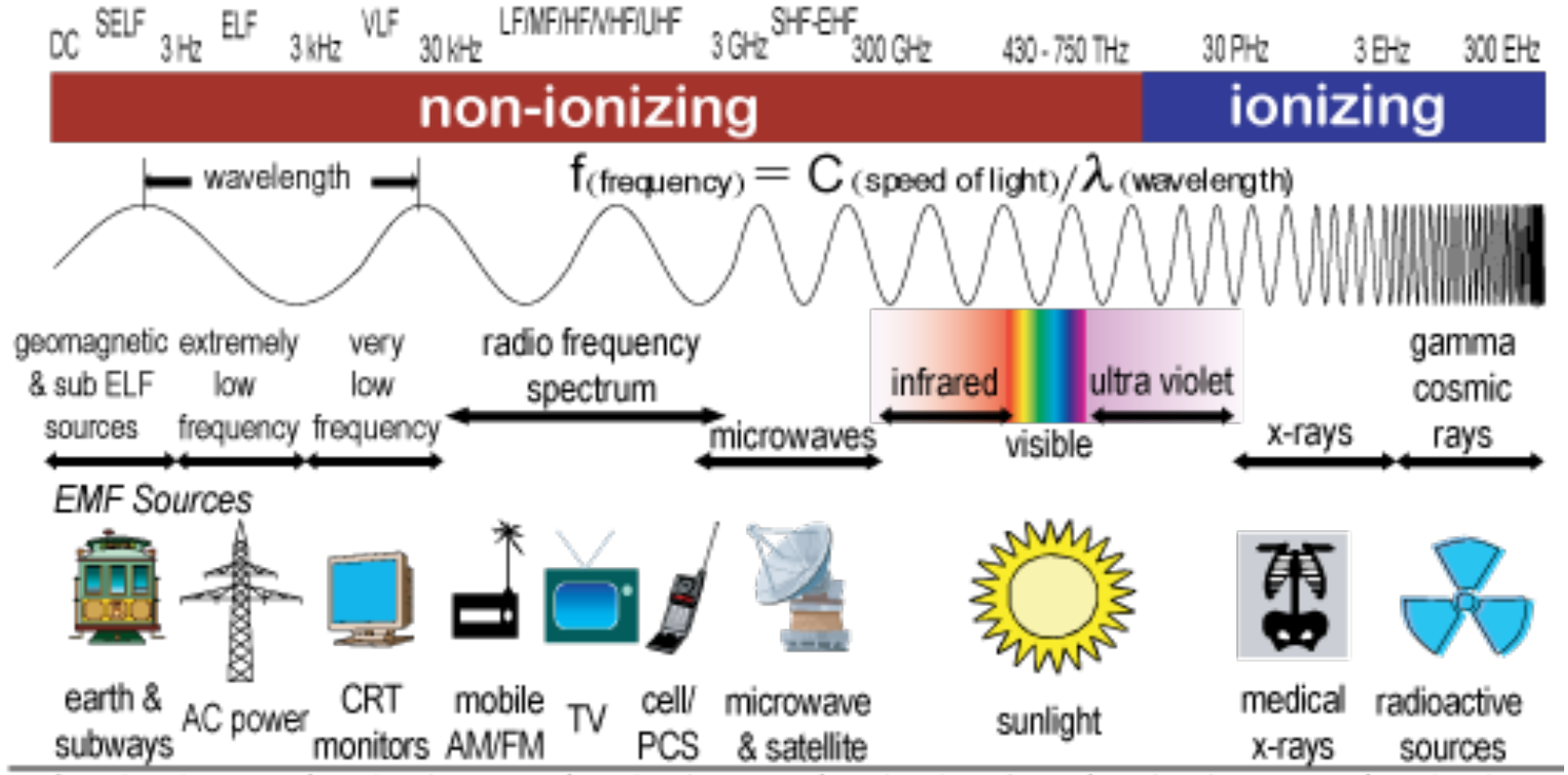
BPDE forms a DNA adduct.

- Incomplete combustion of organic material during smoking are strongly implicated as the carcinogenic component of tobacco smoke.



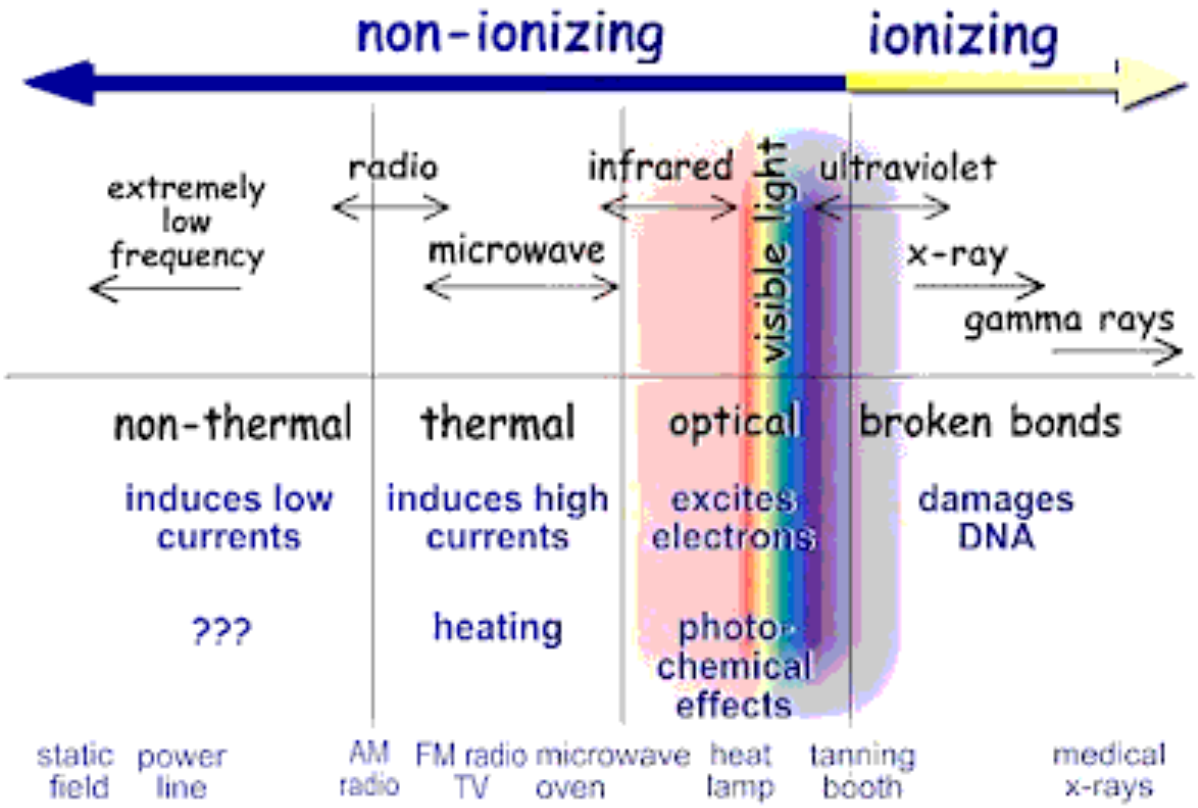
- After ingestion, benzo[a]pyrene is metabolically altered to benzo[a]pyrene diol epoxide, or BPDE, by the P450 pathway.
- BPDE binds directly to DNA and forms four structurally distinct covalent adducts at the N2 position of guanine
- N2-BPDE-dG adducts constitute a significant barrier to advancing DNA replication forks in proliferating cells.
- The repair process that resolves such lesions results in a high proportion of G → T transversion mutations.

THE ELECTROMAGNETIC SPECTRUM



Gigahertz (GHz) 10-9 Terahertz (THz) 10-12 Petahertz (PHz) 10-15 Exahertz (EHz) 10-18 Zettahertz (ZHz) 10-21 Yottahertz (YHz) 10-24

Electromagnetic radiation spectrum



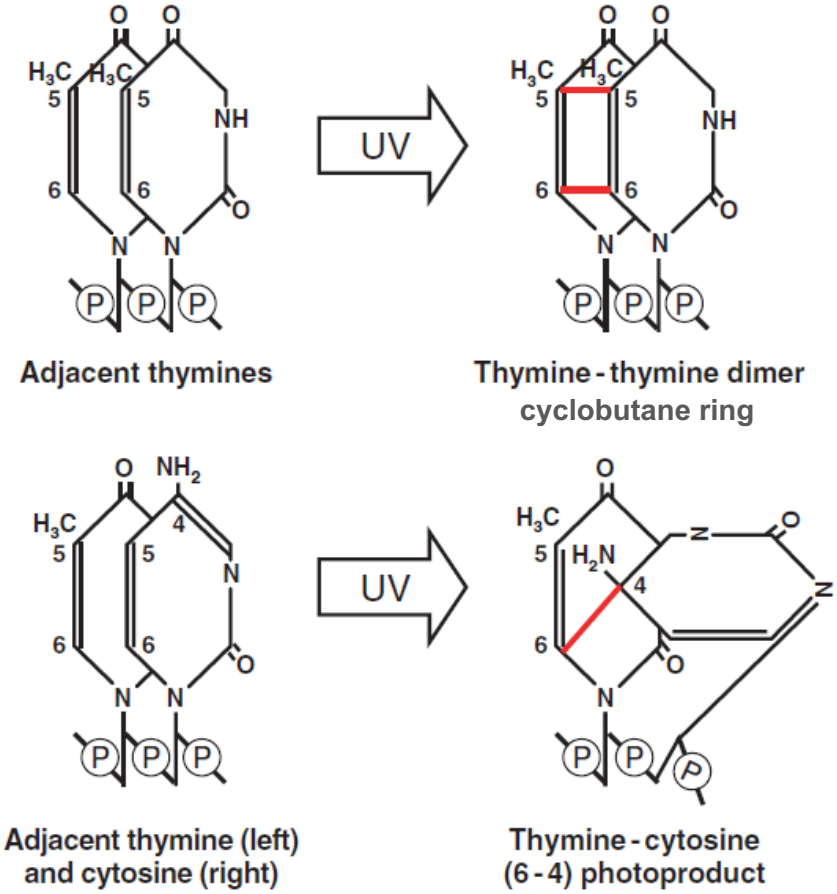
UV-B induced DNA lesions

- 290–320 nm in the electromagnetic spectrum, is a mutagen that causes two types of alterations to adjacent pyrimidines:

  cyclobutane dimers and
  pyrimidine (6–4) pyramidone photoproducts

- Most pyrimidine photoproducts are repaired by nucleotide excision repair. Failure of this DNA repair mechanism results in a single nucleotide substitution (C>T) mostly resides at CpG dinucleotides.

- CC → TT double base mutations observed occur most commonly in the context of the triplet sequence CCG.



- UV-B induced base changes have a unique signature as they mostly occur next to 5mC bases.

Ionizing radiation

- Potent clastogen
- Significantly weaker mutagen (many chromosomal breaks but relatively few mutations propagated by cell divisions)
- NHEJ (non homologous end joining) and homologous recombination repair systems are activated.
- NHEJ repairing causes 1-2% repair errors causing microdeletions

Chronic inflamation and Cancer Predisposition

Infectious agent	Type	Inflammatory disease	Cancer
Hepatitis B virus	DNA virus	Hepatitis	Liver cancer
Hepatitis C virus			
Helicobacter pylori	Bacterium	Gastritis	Stomach cancer
Epstein-Barr virus	DNA virus	Mononucleosis	B-cell, non-Hodgkin's lymphoma
			Burkitts lymphoma
Human Papillomavirus	DNA virus	Cervicitis	Cervical cancer
Schistosoma haematobium	Trematode	Cystitis	Bladder cancer
Opisthorchis viverrini	Flatworm	Cholangitis	Bile duct cancer