Chemical and physical etiological factors in oncogenesis

Physical etiological factors

Physical etiological factors

- Ionizing radiation
- Ultraviolet radiation
- Microwave radiation
- Electromagnetic radiation

- Asbestos
- Nanoparticles

Ionizing radiation

radiation that has enough energy to cause ionization of molecules by displacing electrons from atoms

1) Electromagnetic (X and gamma rays)
2) Corpuscular (electrons, protons, neutrons...)

Data that indicated the role of radiation in oncogenesis:

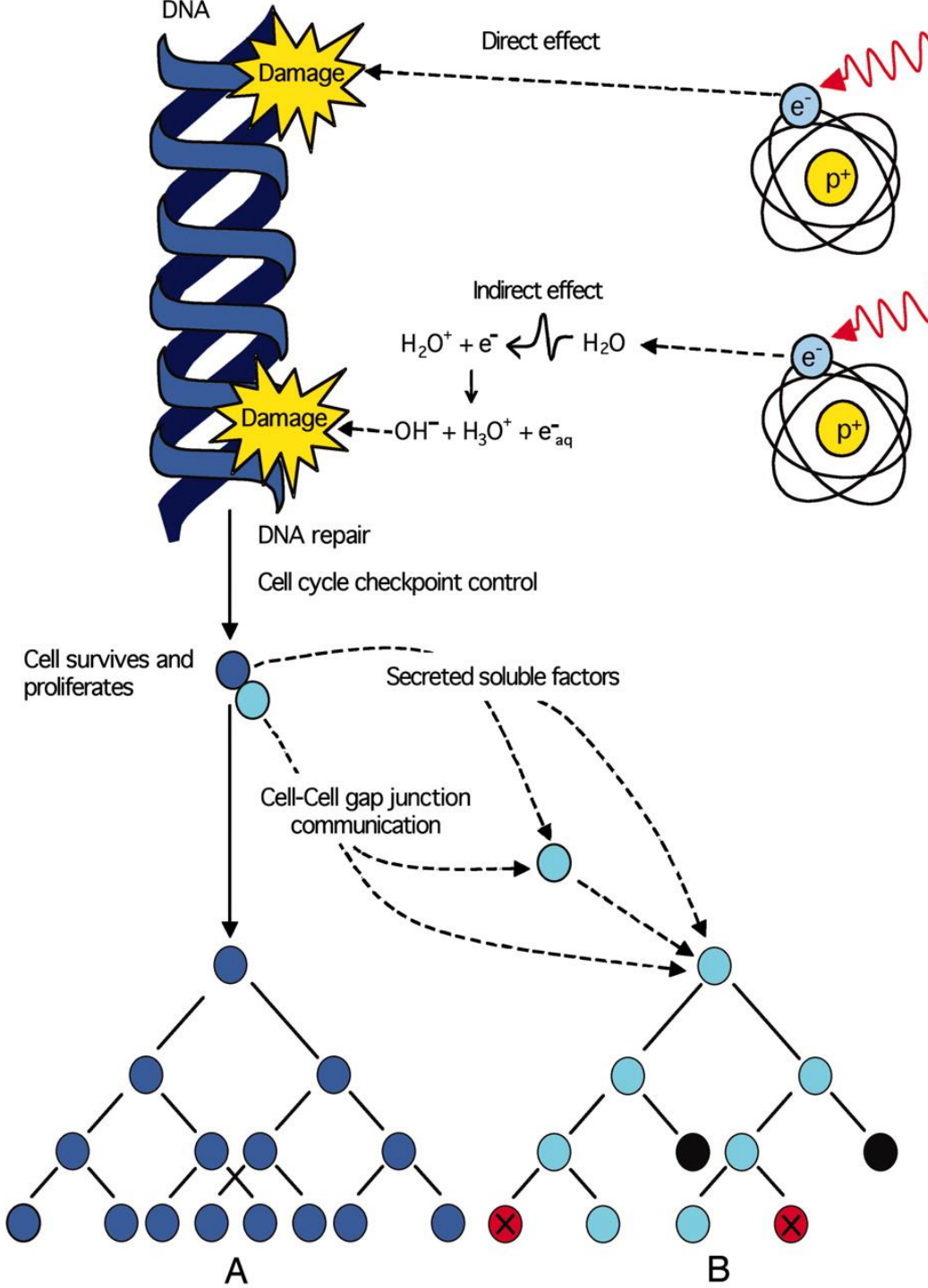
- Higher incidence of skin tumors in health workers professionally exposed to X-ray radiation
- Higher incidence of leukemia among radiologists and health workers who work with radioisotopes
- Increase in neoplasms after the dropping of atomic bombs on Hiroshima and Nagasaki at the end of World War II

Ionizing radiation acts on the DNA molecule

- Directly, causing ionization of the DNA molecule itself

- Indirectly, acting on water molecules that generate free radicals that have enough energy to ionize a DNA molecule

scavengers of free radicals (glutathione) protect the cell from radiation



DNA damage

...wrong pairing of base pairs, missense and nonsense mutations, macrogenetic damage (breaks and deletions of chromosomes)

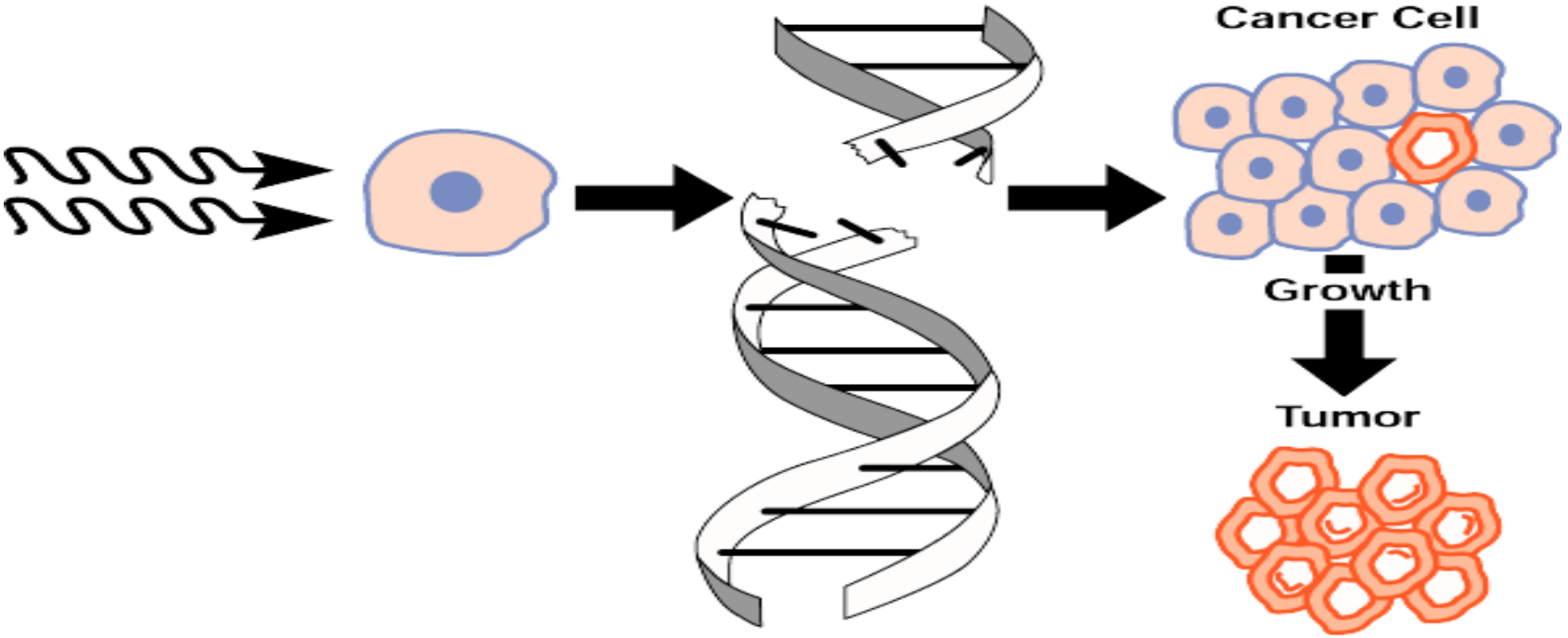
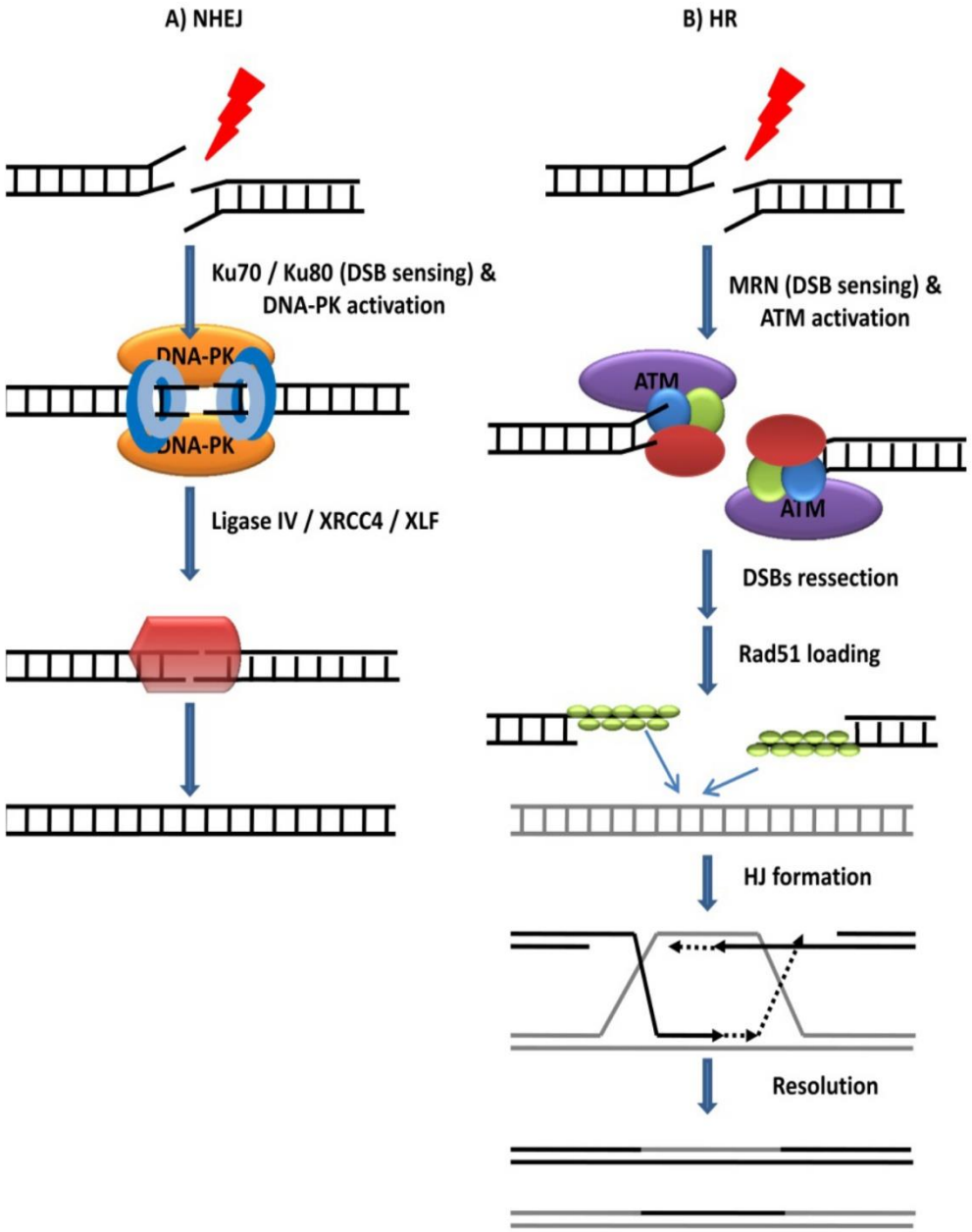


Figure 1. Development of cancer from mutation produced by ionizing radiation.

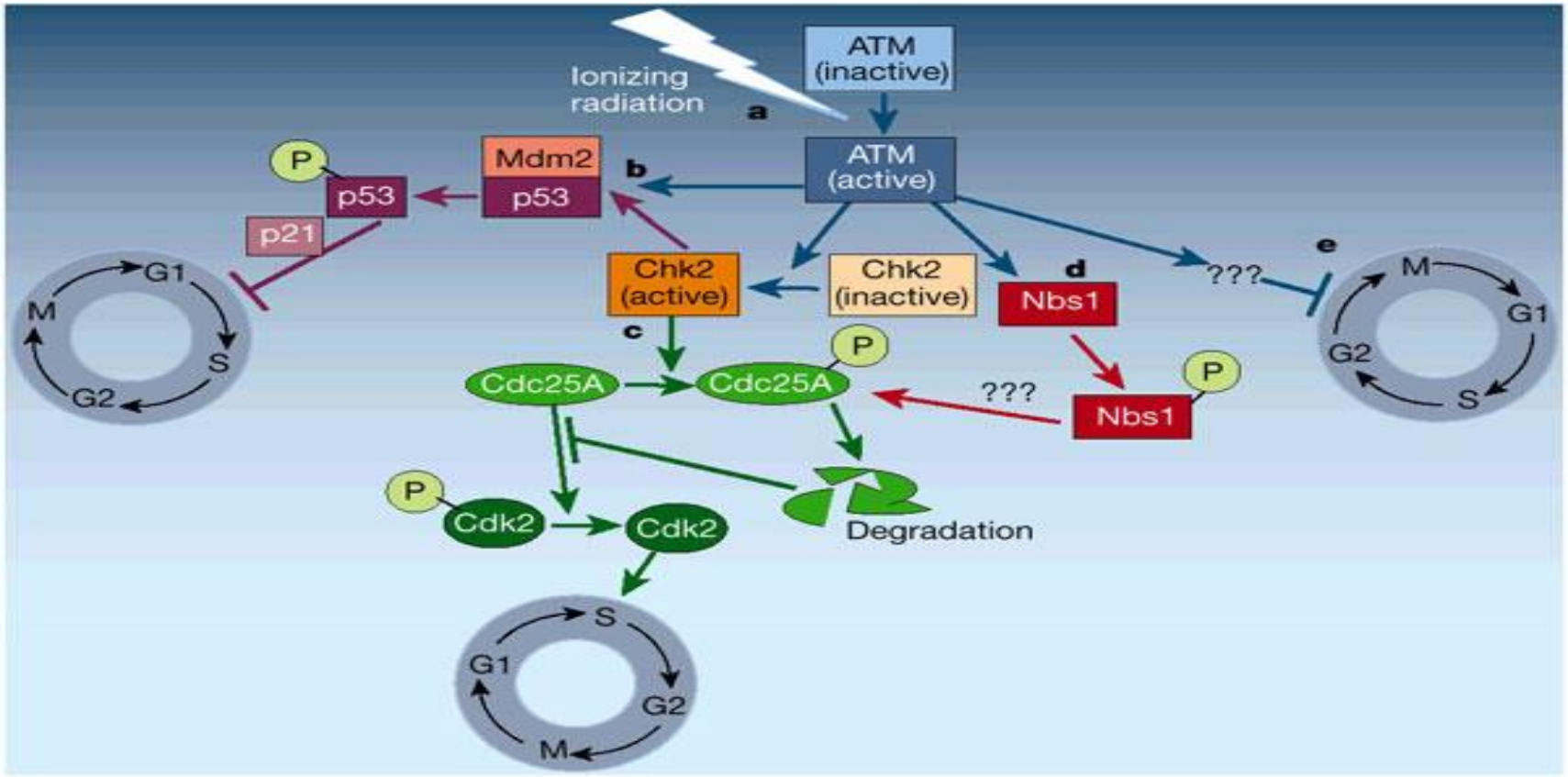
Expression and function of many proto-oncogenes and tumor-suppressor genes changes, which forms the basis of malignant cell transformation

Reparative processes in the cell



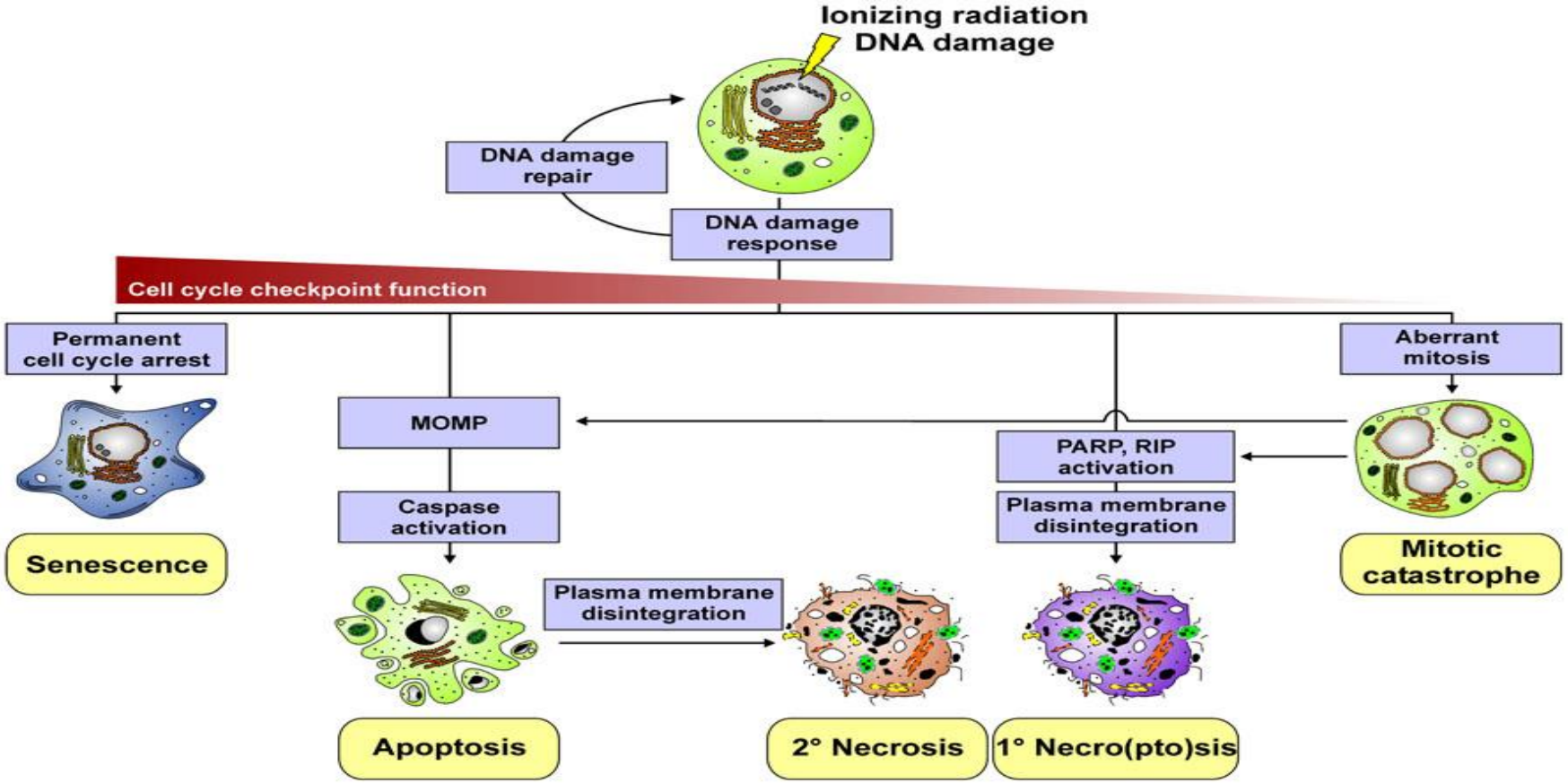
A) Non-homologous end pairing: DNA breaks are detected by Ku70/Ku80 heterodimers that stabilize the ends and recruit DNA-PK. DNA-PK phosphorylates and activates the effector complex (ligase IV/XRC44/XLF) that repairs damaged DNA **B) homologous recombination**. ATM kinase is activated, which phosphorylates numerous substrates. A number of endo- and exo-nucleases (Mre11, Exo1 and CtIP) correct double-stranded DNA breaks and make single-stranded DNA that attract Rad51. Rad51 forms homologous junctional segments.

Cellular response to damage



Ionizing radiation activates the kinase ATM which then activates the kinase Chk2. b, which affects the blockade of the transition from the G1 phase to the S phase by phosphorylating and stabilizing the p53 protein, which enhances the expression of the cell cycle inhibitor p21. c, Activation of Chk2 and ATM affects S phase progression by phosphorylating Cdc25A. When Cdc25A is unphosphorylated it removes the phosphate group from Cdk2 thus allowing initiation of DNA replication d, Nbs1 is phosphorylated by the activity of ATM which is involved in radiation induced inhibition of S phase progression.

Radiation-induced cell death



p53-dependent and later p53-independent apoptosis occurs apoptosis necrosis - DNA damage, especially if combined with hyperthermia, induces hyperactivation of the DNA repair enzyme PARP, which is followed by depletion of ATR and activation of necrosomes - necrosis/necroptosis senescence-permanent cell cycle arrest, while checkpoints are intact mitotic catastrophe - aberrant mitosis, the formation of giant cells that live for several days and die by apoptosis or necrosis

Ionizing radiation

tissue sensitivity

- The most common are hematopoietic tissue neoplasms and solid tumors of the thyroid gland, breast, and lungs
- Tumors of the colon, stomach, liver, ovaries, and urinary bladder are somewhat rarer
- Very rare bone tumors and sarcomas
- There is no evidence that tumors of the pancreas, cervix, prostate and small intestine can be caused by radiation

Ionizing radiation

latent period

the period from the moment of exposure to the appearance of the tumor

- Shorter for hematopoietic tissue neoplasms (about 2 years)
- Longer for solid tumors (5 - 10 years)

The length of the latent period is influenced by other factors: radiation dose, age, etc.

Ionizing radiation

the risk depends on the dose of radiation

- Small and frequent doses act cumulatively (CT, mammography, etc.)
- Large single dose

Age of the patient - children and adolescents have a 10-15x higher risk

Genetic predispositions and genetic instability

- Down's syndrome, ataxia-telangiectasia

Previous applications of radiotherapy

- Often in the treatment of childhood cancer, Hodgkin's disease, breast cancer, bone marrow transplantation

Ultraviolet radiation

does not have enough energy to cause ionization of molecules, passing through living matter excites molecules, which by absorbing energy pass into a more reactive state and more easily enter into chemical reactions with other molecules

Based on wavelength, there are three types of ultraviolet radiation:

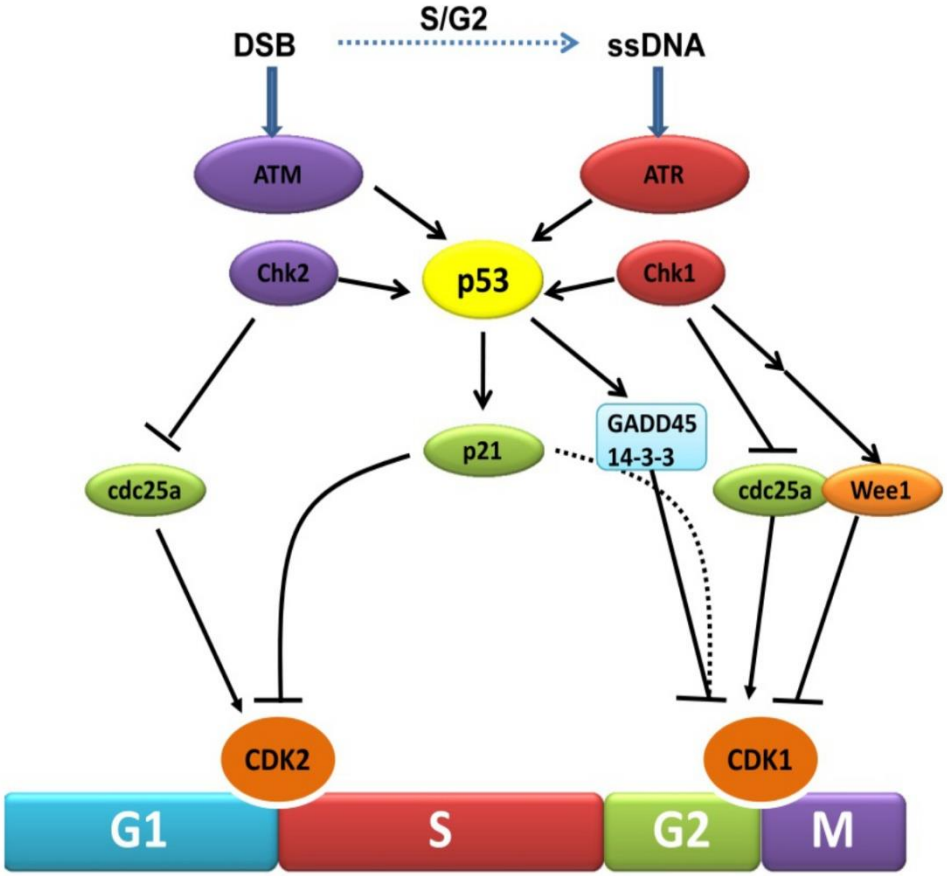
wavelengths from 240 to 290 nanometers ("**UVC**");
wavelengths from 290 to 320 nanometers ("**UVB**");
wavelengths from 320 to 400 nanometers ("**UVA**").

Ultraviolet radiation
mechanism of DNA damage

- UVC and UVB changes the position of double bonds, dimers of pyrimidine bases and a cyclobutane ring (6-4 photoproducts) are created.
- These products interfere with the normal synthesis of DNA and RNA and have a mutagenic and carcinogenic effect
- UVA radiation causes the production of free radicals capable of causing DNA damage.

Ultraviolet radiation
Cell ansfer

- Repair mechanism: nucleotide excision and removal of pyrimidine dimers and photoproducts (recognition of the change in DNA, nucleases cut DNA and DNA polymerases synthesize new nucleotides.
- UV radiation acting on proliferating cells activates both ATM and ATR kinases, whose substrates are p53 and ChK1, which cause cell cycle arrest in S or G2 phase. This radiation can also directly activate membrane receptors, causing their phosphorylation and transmission of signals that affect proliferation



Ultraviolet radiation
Cell death

UV rays induce cell apoptosis in several ways...

Disturbed RNA synthesis due to the effect of radiation is the main cause of apoptosis

Action on p53 can also induce apoptosis, although activation of this protein protects fibroblasts and keratinocytes from apoptosis

Cell death can also be induced by direct activation of FAS molecules by UV rays

Ultraviolet radiation

Skin tumors

Non-melanoma skin tumors usually appear on the head, neck and extremities, ie. parts of the skin that are directly exposed to the long-term effect of radiation (pigmented skin is less sensitive to the effect of ultraviolet radiation). Melanoma tumors are not usually associated with anatomical locations that are chronically exposed to ultraviolet rays, but the risk of developing melanoma tumors increases after acute burns caused by exposure to ultraviolet rays.
xeroderma pigmentosum

Microwave radiation

radiation frequency 300 MHz - 300GHz
sources are mobile phones, wireless internet devices, kitchen appliances, radars

- it does not cause tissue ionization, it turns into heat
- absorbed heat can subsequently induce free radical generation and induce DNA damage in human spermatozoa in vitro
- causes p35/MAPK pathway phosphorylation

Conflicting findings about the role in tumor formation

Electromagnetic radiation

- It does not directly cause DNA damage, but has been shown to interfere with DNA replication and thus induce cell apoptosis.
- It also has non-genotoxic effects, it interferes with signaling pathways in cells, but the biological consequences of this effect are not yet known.
- There is a strong correlation between exposure to electromagnetic radiation and the occurrence of leukemias, brain tumors, and breast tumors.

Asbestos

exposure to asbestos is associated with the risk of developing tumors (shown in 1935)

- Asbestos fibers enter the cell and induce the formation of free radicals, especially in cells that contain a lot of iron.
- 8-Hydroxyguanine and DNA breaks, chromosomal aberrations are formed.
- Numerous signaling pathways in the cell MAPK, EGFR, NFκB are activated which induces inflammation, enhances cell proliferation, and increased expression of TGFβ stimulates fibrogenesis.
- Epidemiological studies have shown that asbestosis increases the risk of developing lung and pleural tumors.

Nanoparticles

particles with a diameter of 1-100 nm

- The cellular effects of nanoparticles are similar to the effects of asbestos, they induce the appearance of free radicals in the cell and inflammation.
- ATM and ATR kinases are activated
- Proinflammatory cytokines, TNFα, are released.
- Nanoparticle, titanium dioxide, used to make paint is classified as a substance that may play a role in the development of lung and pleural tumors (although there are no data from epidemiological studies yet).

Chemical etiological factors

- Aksoy: 1971-1985. acute leukemias are more frequent 10h in persons who were professionally exposed to benzene
- Changes in the incidence of certain tumors among ethnic groups after migration
- Significant increase in the number of malignant diseases among smokers

Confirmation of the role of chemical etiological factors in oncogenesis was also obtained using numerous data from experiments on animals or in cell cultures.

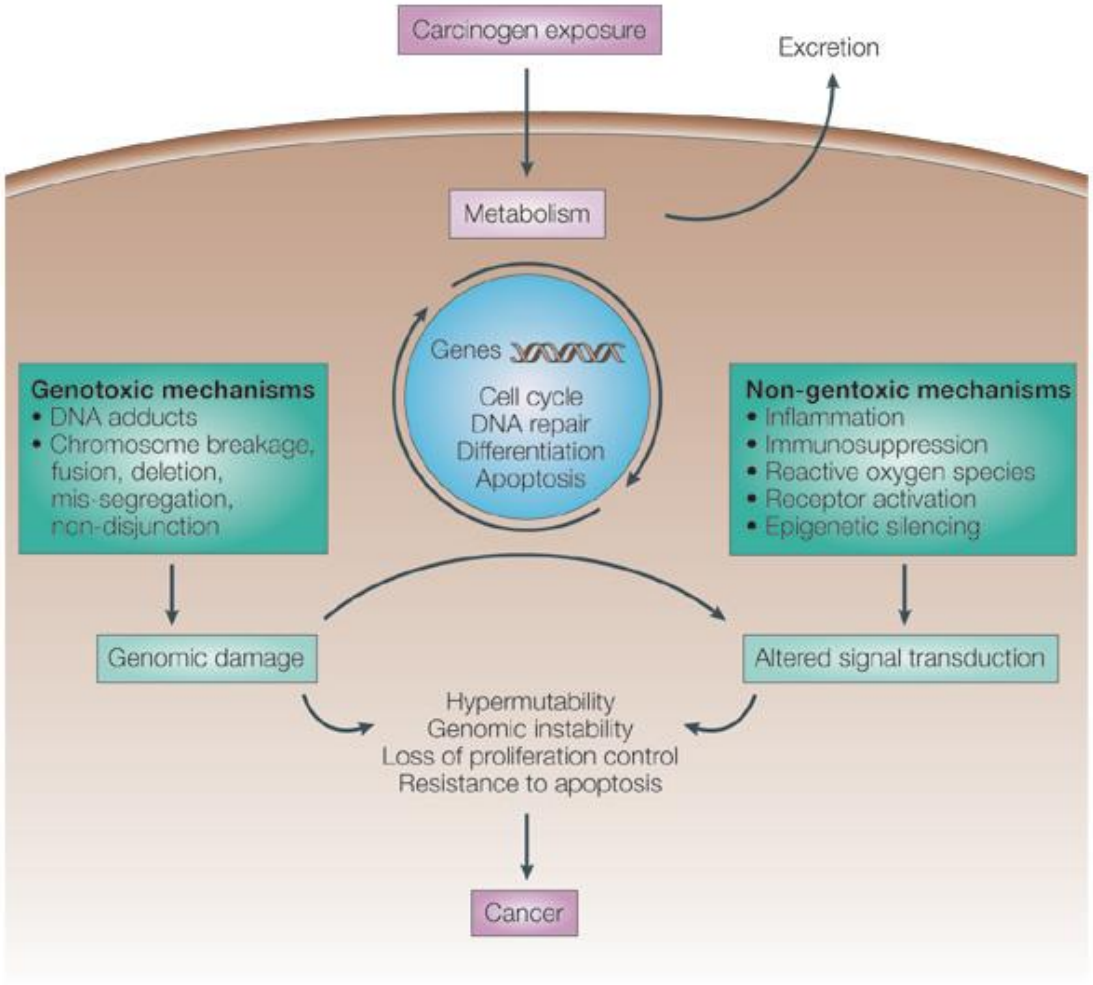
Chemical carcinogens and the risk of tumor occurrence in the human population

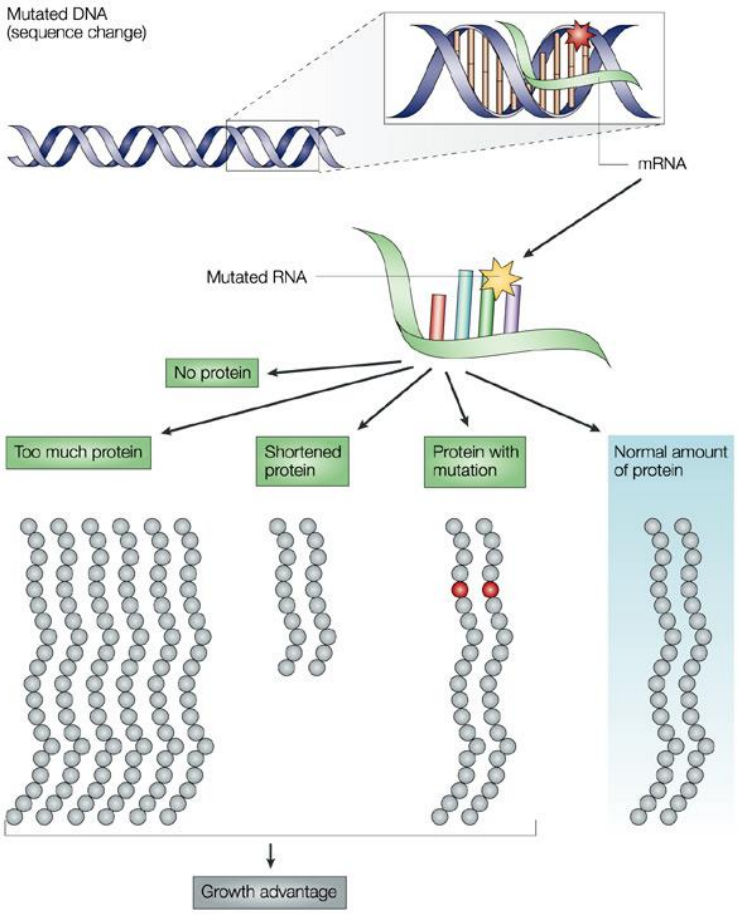
Organ	Agens	Industry	Tumor type
Lungs	Tobacco smoke, arsenic, asbestos, benzopyrene, beryllium, silk, 1,2-butadiene, chromium-IV compounds, tar, nickel, mustard gas	Aluminum production, gasification of gas, hematite mines, painters	Squamous, small cell, large cell, adenocarcinoma
Pleura	Asbestos	Inhalation, mining	Mesothelioma
Oral cavity	Tobacco smoke, alcohol	-	Squamous cell carcinoma
Esophagus	Tobacco smoke, alcohol	-	Squamous cell carcinoma
Stomach	Smoked, salty and canned food	Rubber industry	Adenocarcinoma
Colon	Heterocyclic amines, asbestosis		Adenocarcinoma
Liver	Aflatoxin, vinyl chloride, alcohol, tobacco smoke	-	Hepatocellular carcinoma, hemangioma
Kidneys	Tobacco smoke, phenacetin	-	Kidney cancer
Prostate	Cadmium	-	adenocarcinoma
Skin	Arsenic, benzopyrene, tar, mineral oils, cyclosporine, PUVA	Gasification of gas	Squamous cell carcinoma, basal cell carcinoma
Bone marrow	Benzene, tobacco smoke, ethylene oxide, antineoplastic agents, ciclosporin		Leukemia, lymphoma

Chemical etiological factors

Genotoxic: they act directly on DNA.
Transfer an alkyl or aryl group to DNA (alkylating agents, aliphatic epoxides, nitroso compounds, polycyclic hydrocarbons, numerous ingredients of food and mineral oils)
Transfer the arylamine group to the DNA molecule (aryl-aromatic amines, amino-azides and heterocyclic aromatic amines)
Non-genotoxic: they work through different mechanisms: through free radicals, they imitate the action of hormones, etc.

Chemical etiological factors





Both genotoxic and nongenotoxic agents can act on oncogenesis by inducing DNA and histone methylation or by acting on other processes involved in transcription.

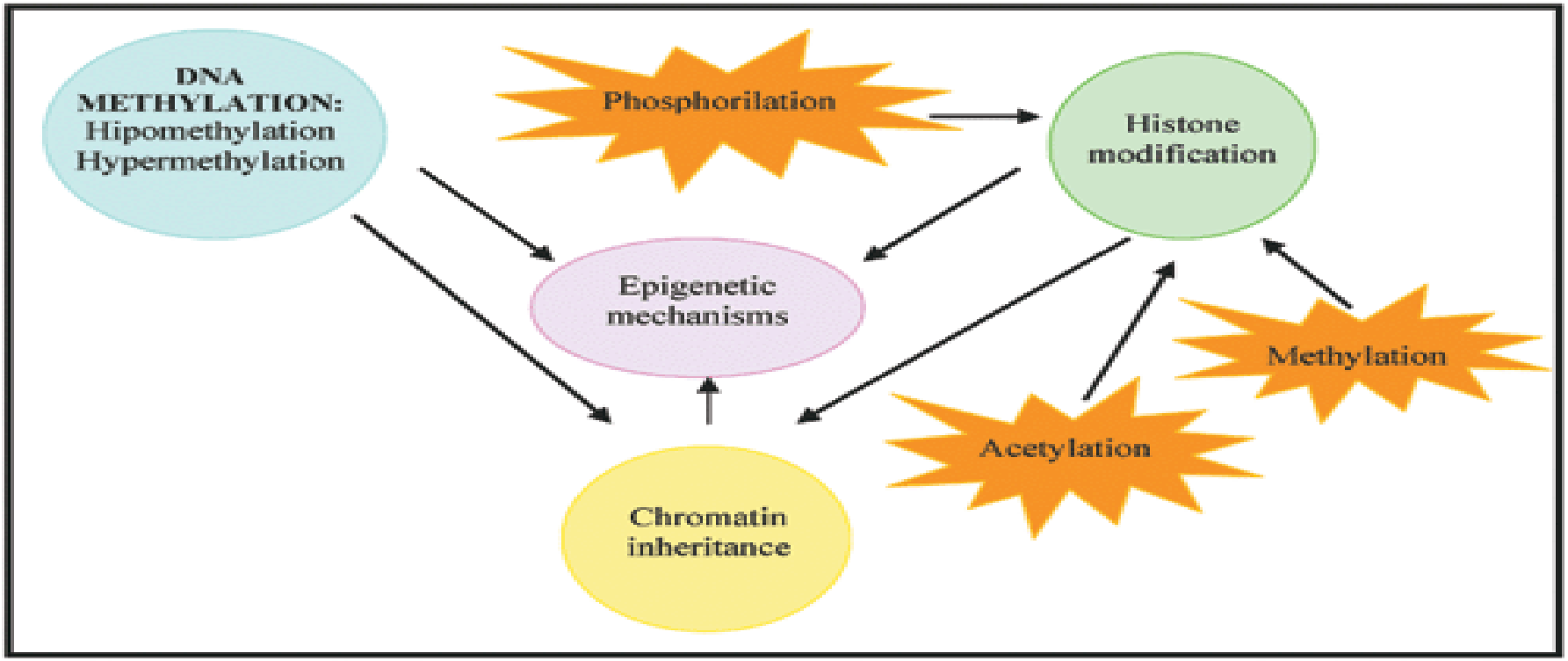


Fig. 5 – Epigenetic mechanisms involved in chemical carcinogenesis.

Permanent epigenetic change is an important factor in carcinogenesis.

Reparative processes in the cell

DNA repair generally involves removing the DNA-carcinogen bond mainly on the strand that serves as a template for transcription in order to prevent the synthesis of the mutant protein

Most human tumors are not a simple, genetically determined, consequence of aging, but are the result of individual exposures (exogenous and endogenous) to other factors that enhance genetic predisposition.

The relationship between tobacco smoke and oncogenesis

cancer of the lung, bladder, esophagus, kidney, larynx, pancreas, oropharyngeal region and stomach

- Tobacco smoke contains more than 20 carcinogenic substances, polycyclic hydrocarbons, nitrosamines, aromatic amines, ethylene dioxide, 1,3-butadienes
- The risk of developing lung cancer is influenced by the number of cigarettes used during the day, the number of years of smoking, the type of cigarettes and the way of smoking (how deep the tobacco smoke enters the bronchial tree).
- We should not forget the genetically determined predisposition that is reflected in the metabolism of carcinogens, the repair of damaged DNA and the control of the cell cycle.