Fundamentals of radiation biochemistry. Incorporated radionuclides. Carcinogenesis.

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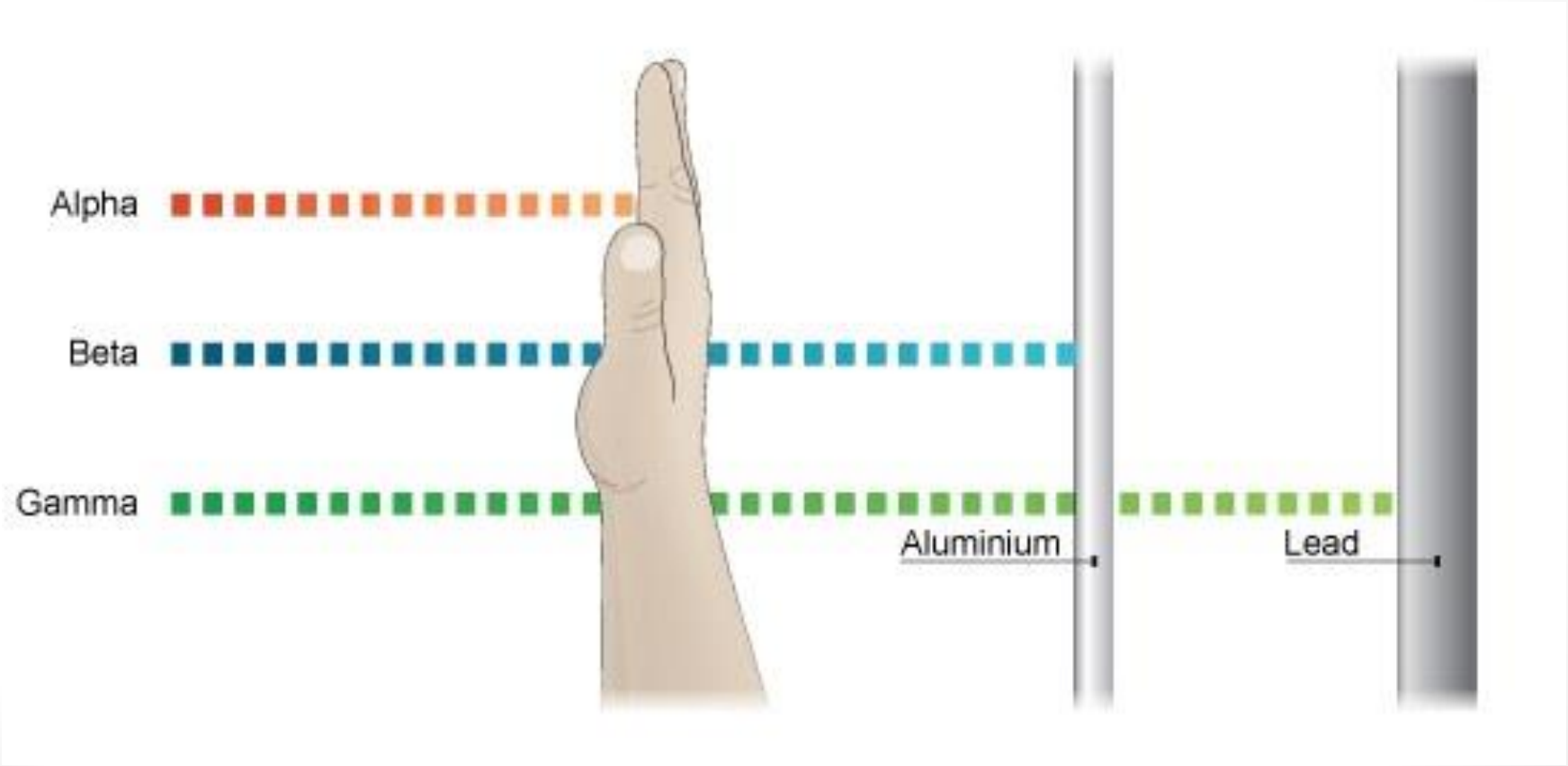
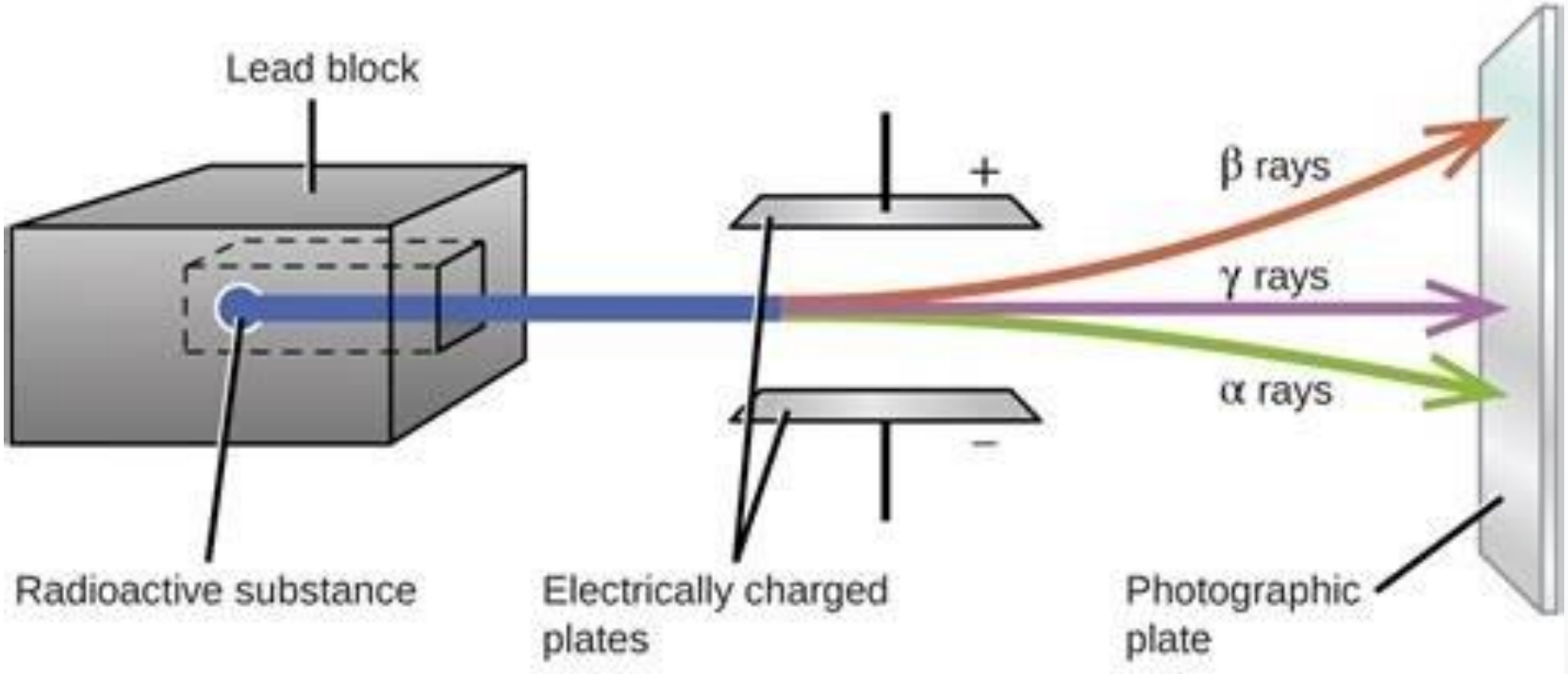
Interaction of ionizing radiation with living tissue



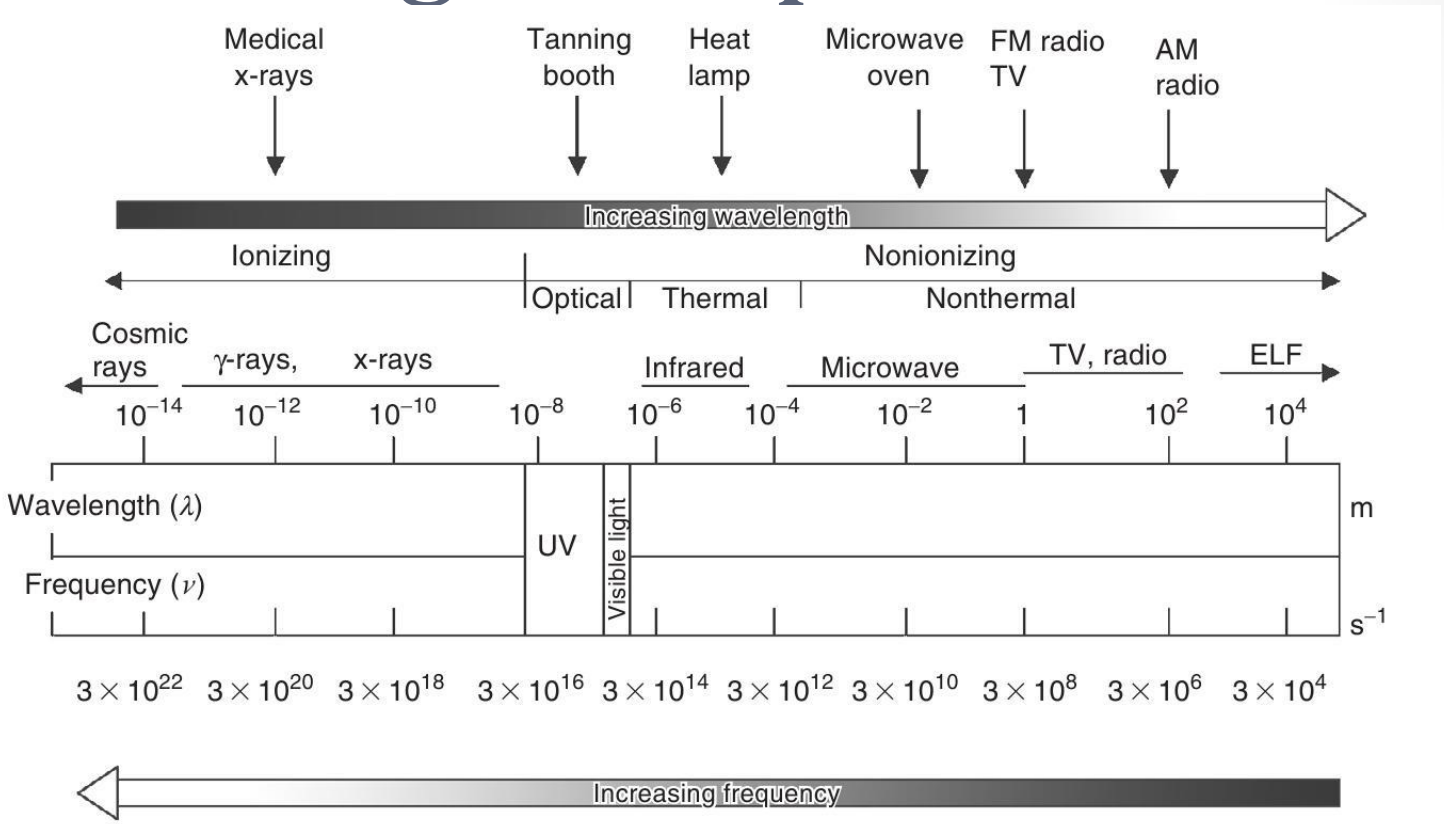
Types of radiation: electromagnetic and corpuscular



Electromagnetic Radiation

- Experiments with biological systems and most clinical applications involve either x-rays or gamma (γ)-rays, two forms of EM radiation with similar properties.
  - The designations, x-ray or γ-ray, depend on the way by which they are produced.
  - **x-Rays** are produced in an x-ray tube when accelerated electrons hit a tungsten target and then decelerate, emitting a spectrum of **bremsstrahlung radiation** as part of the kinetic energy (KE) of the electrons which is converted into x-rays. The resulting spectrum is filtered and otherwise modulated to produce a clinically useful x-ray beam.
  - **γ-Rays** are produced spontaneously. They are emitted by radioactive isotopes and represent excess energy that is given off as the unstable nucleus breaks up and decays as it reverts to a stable form.
- x-Rays and γ-rays are part of the continuous spectrum of EM radiation that includes radio waves, heat, and visible and ultraviolet (UV) light

Electromagnetic spectrum



- Electromagnetic spectrum showing relationship between wavelength (m) and frequency (s^{-1}).
- Bands in the spectrum and their characteristics are indicated.

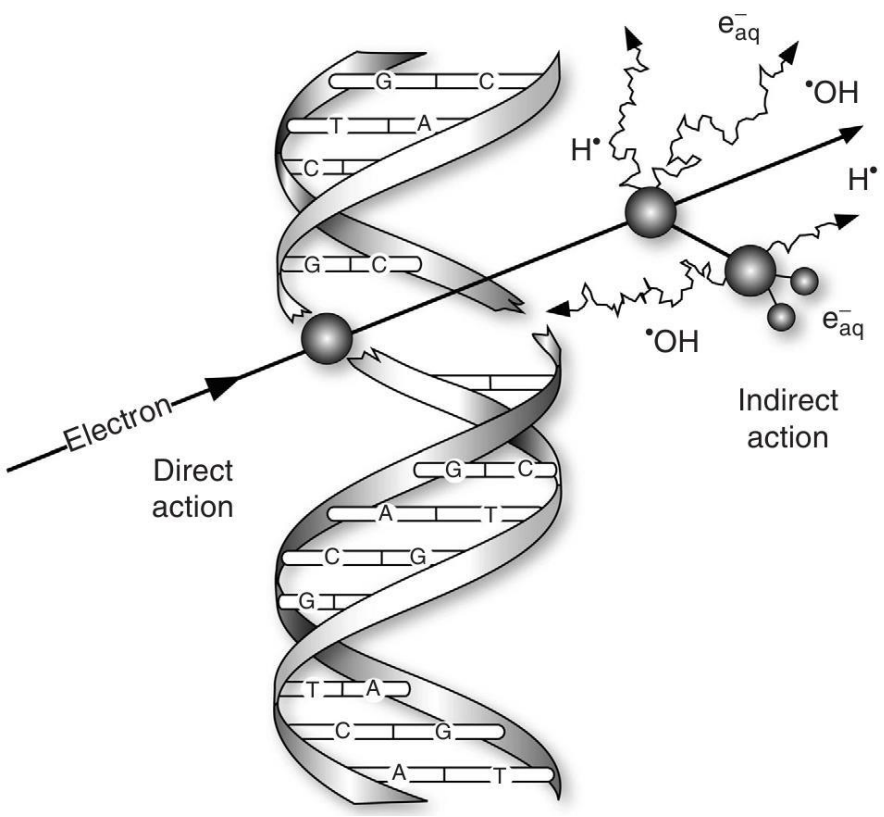
Particulate Radiations (1/2)

- Other types of radiation that occur in nature and also are used experimentally and in some cases clinically are electrons, protons, α-particles, neutrons, negative π-mesons, and heavy charged ions.
- **Electrons** are small, negatively charged particles that can be accelerated to high energy to a speed close to that of light by means of an electrical device such as a betatron or linear accelerator. They are used in the treatment of cancer.
- **Protons** are positively charged particles having a mass 1860 times greater than that of an electron. Because of their mass they require complex and expensive equipment, such as a cyclotron, to accelerate them to useful energies. Naturally occurring protons originating from the Sun represent part of the natural background radiation. The surface of the Earth is protected by the atmosphere and the Earth's magnetic field which deflects charged particles, but protons still remain a major hazard to long-range space missions.

Particulate Radiations (1/2)

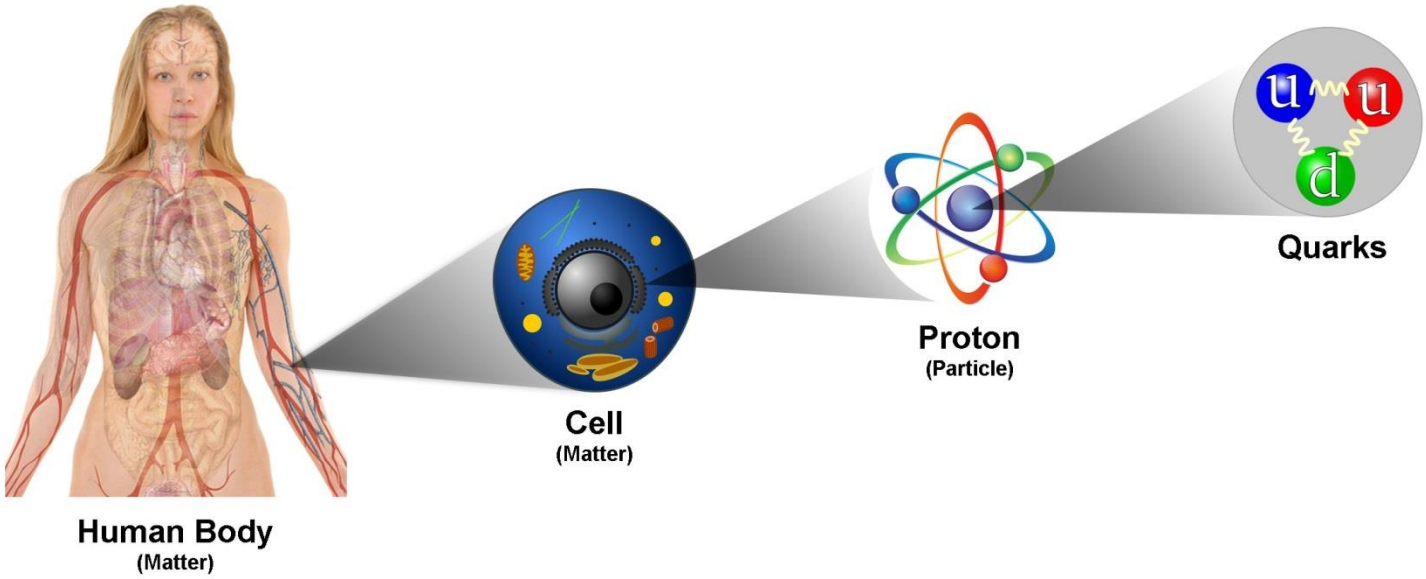
- **α-Particles** are nuclei of helium atoms consisting of two protons and two neutrons. They have a net positive charge and can therefore be accelerated with very large machines similar to those used to accelerate protons. α-Particles are also emitted during the decay of naturally occurring heavy radionuclides, such as uranium and radium.
- **Neutrons** are uncharged particles with a mass similar to that of a proton. Since they are electrically neutral, they cannot be accelerated in an electrical device but they can be produced artificially when a charged particle, such as a deuteron, is accelerated to high energy and strikes a suitable target material (a deuteron is a nucleus of deuterium and consists of a closely associated proton and a neutron).
- Neutrons are emitted when radioactive isotopes of heavy elements undergo fission, and consequently are present in large quantities in nuclear reactors, and they are also emitted by some artificially syn thesized heavy radionuclides. Neutrons are important components of space radiation and contribute significantly to the exposure of passengers and crew of high-flying aircraft.

Direct and indirect action of radiation

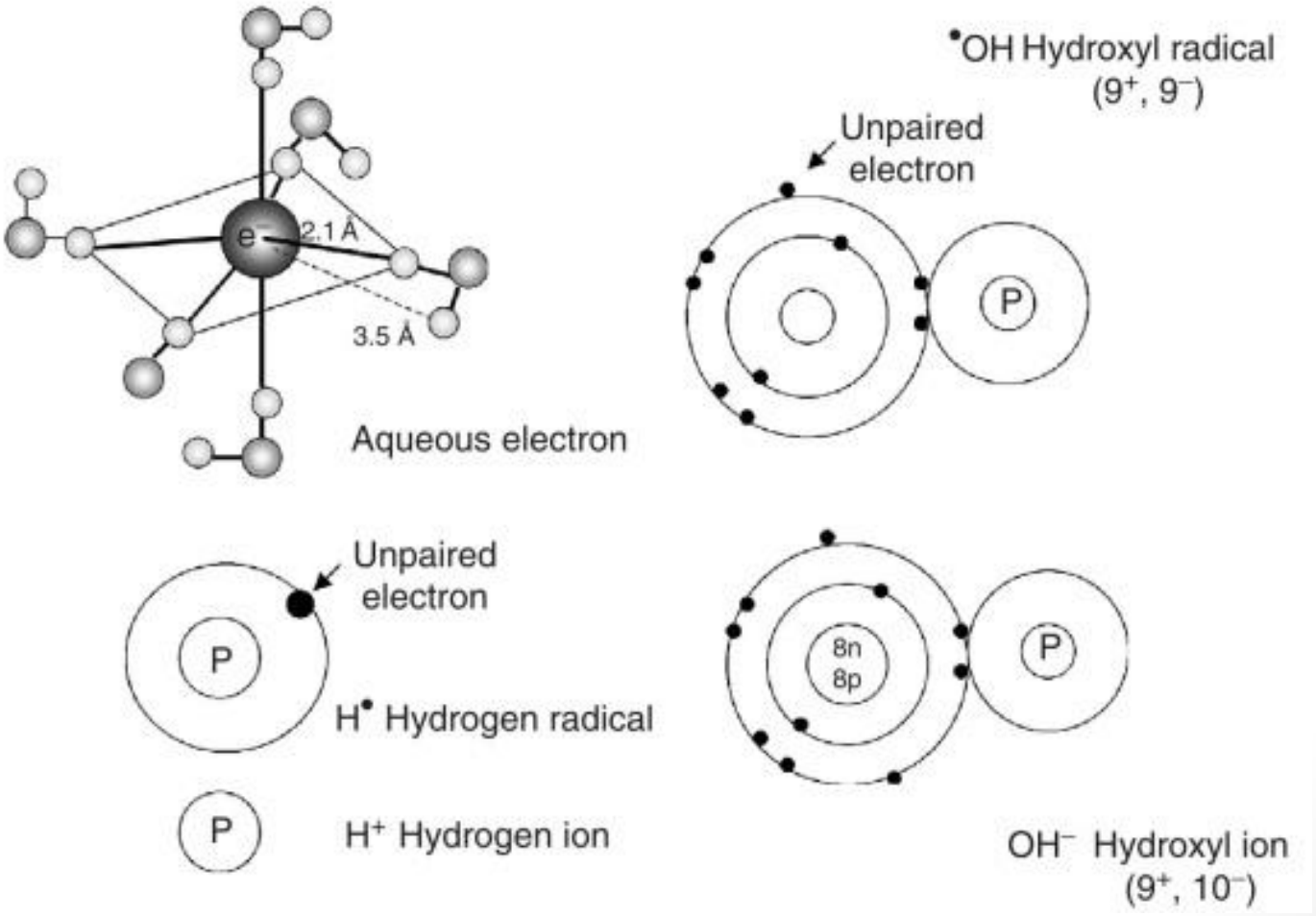


- Any form of radiation, photons, neutrons, or charged particles, may interact directly with target structures causing ionization or excitation, thus initiating the chain of events that leads to a biological change.
- The direct action of radiation is the dominant process for radiations with high linear energy transfer (LET), such as neutrons or α-particles.

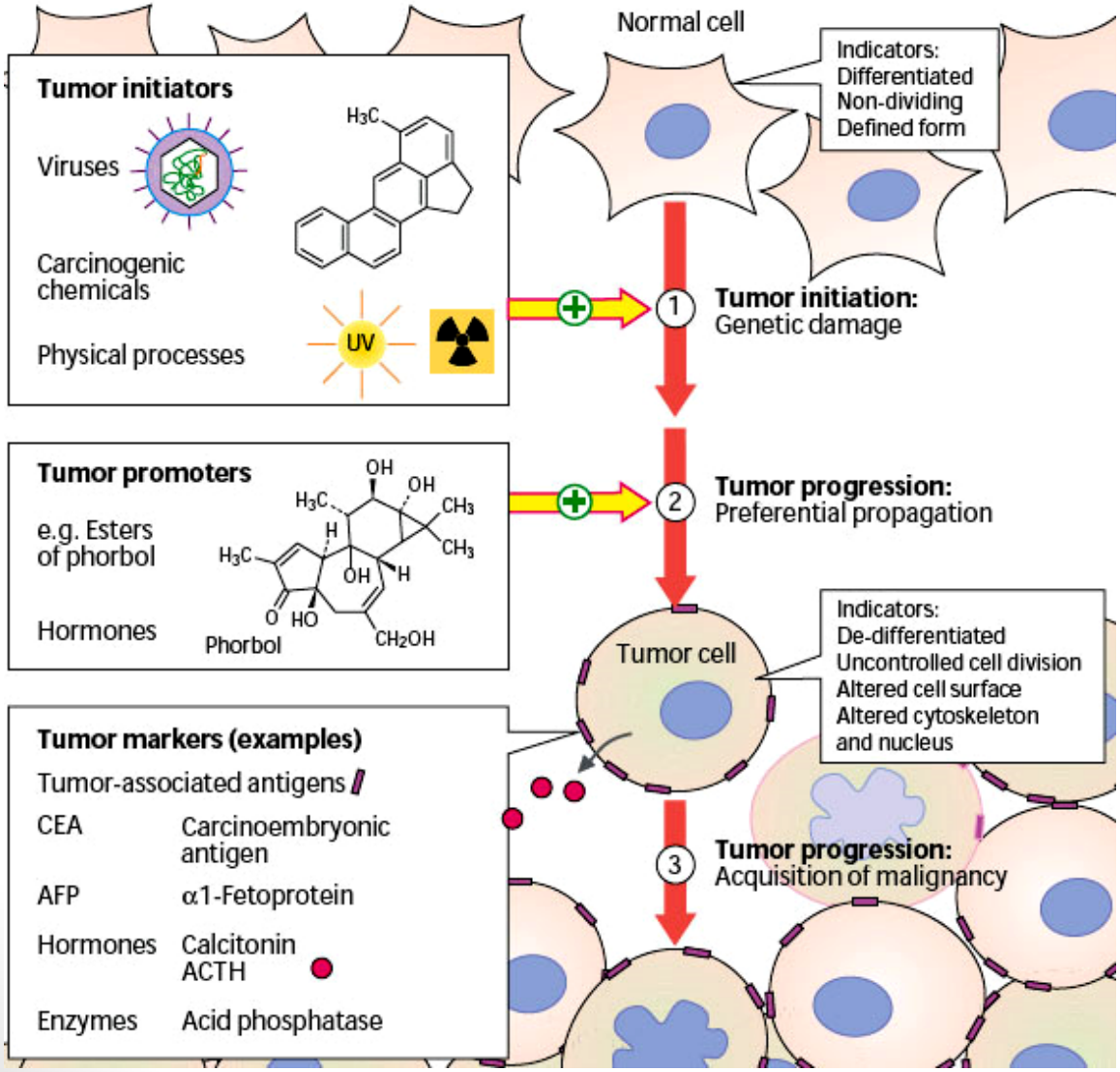
Molecular mechanisms of action of various types of radiation on cells and tissues



Formation of free radicals as a basis for the pathogenesis of radiation damage



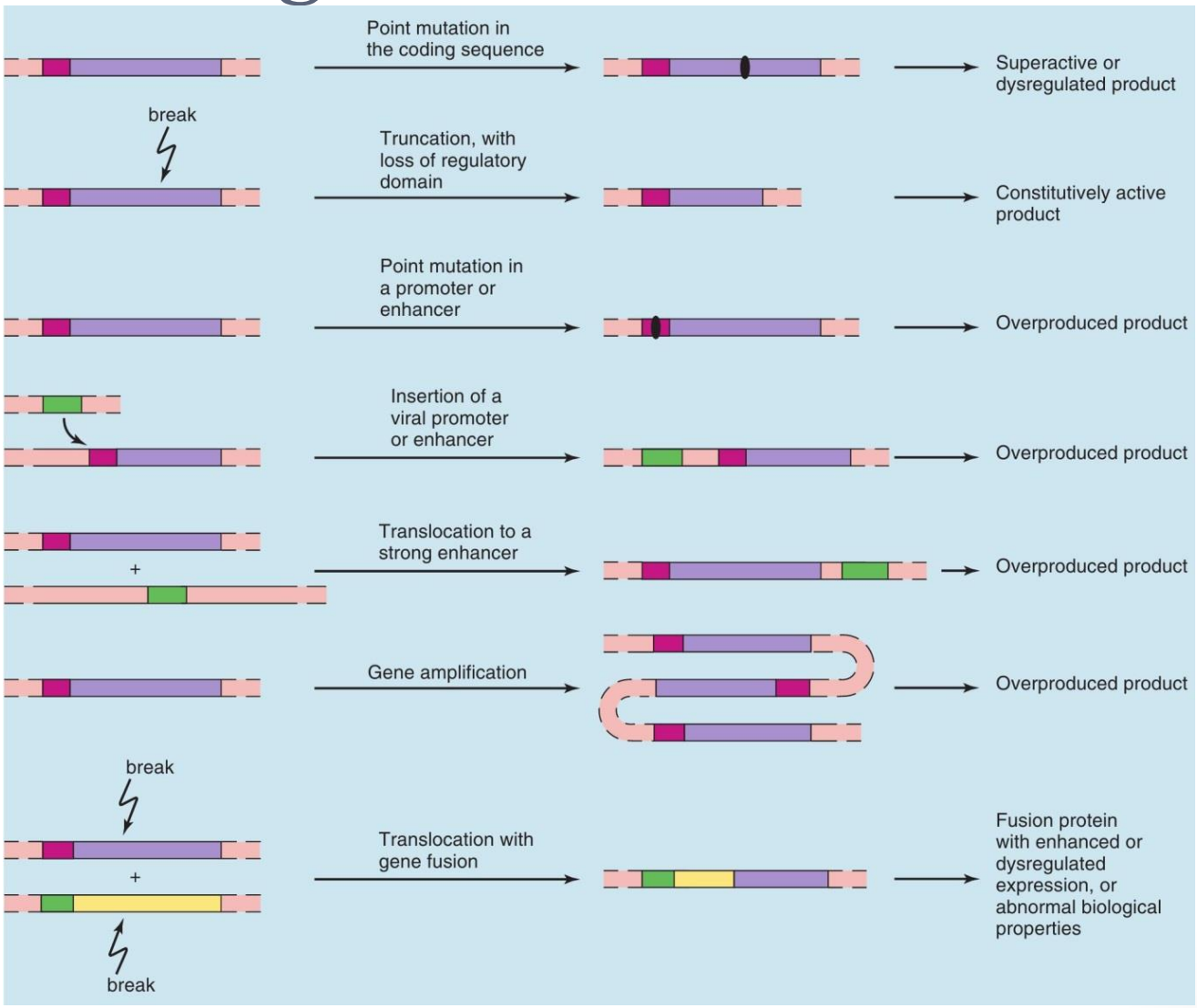
Transformation



Oncogenes and protooncogenes

- Oncogenes are mutated in ways that render the gene constitutively active or active under conditions in which the wild-type gene is not.
- Oncogene activations can result from chromosomal translocations, from gene amplifications or from subtle intragenic mutations affecting crucial residues that regulate the activity of the gene product.
- For example, the most common activating mutation of BRAF in human cancers changes a valine to a glutamate at codon 599, a residue within the activation loop of the kinase domain.
- The activation loop is normally regulated by phosphorylation at adjacent residues (Thr598 and Ser601).
- This suggests that the glutamate substitution at codon 599 mimics a phosphate group and constitutively activates the enzyme even in the absence of signals that would normally result in phosphorylation of the adjacent threonine or serine residues.
- The activated BRAF kinase then phosphorylates downstream targets such as extracellular signal–regulated kinase (ERK), leading to aberrant growth.

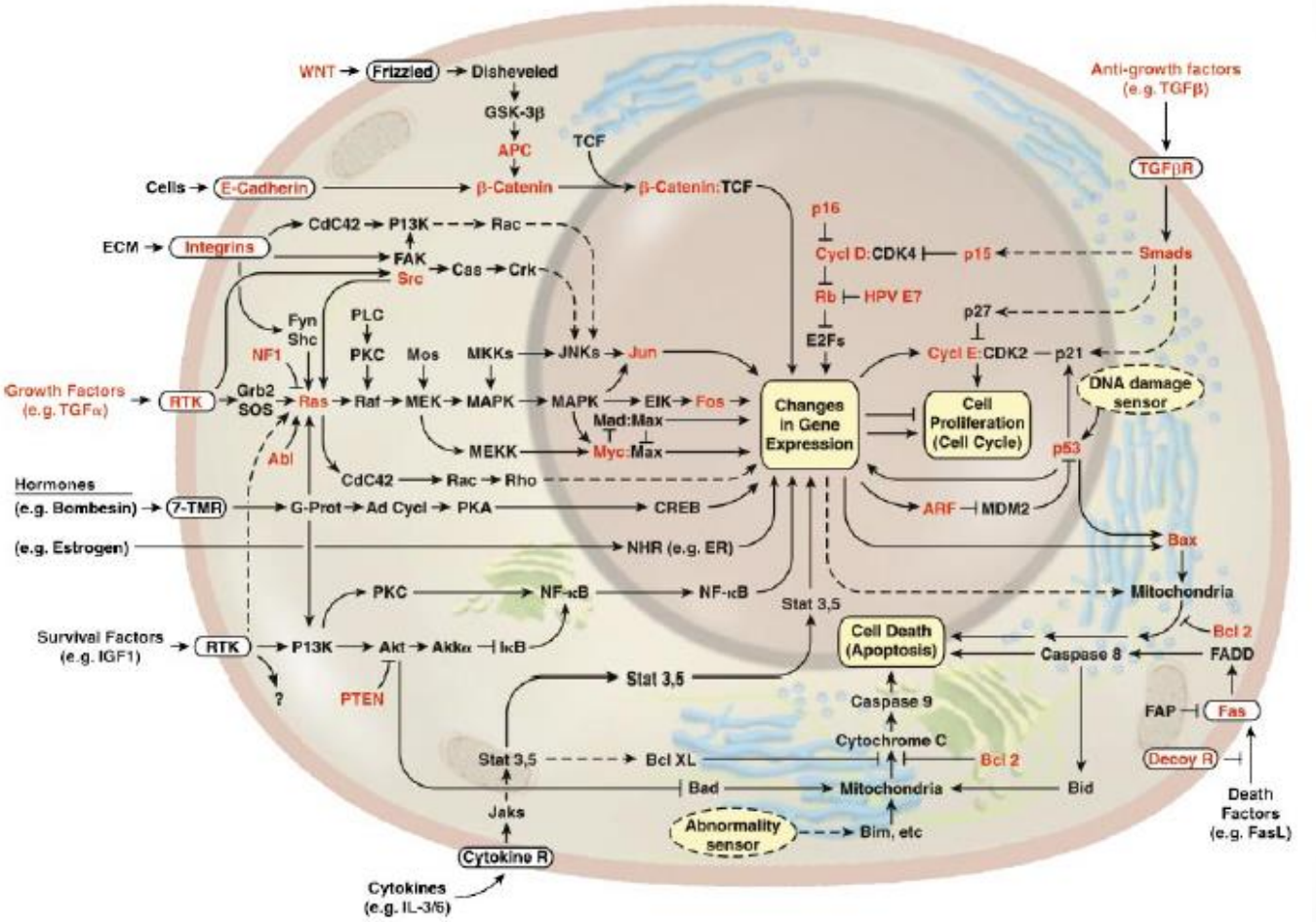
Mutations and activation in protooncogenes



3 different types of mutations

- A **mutation in an oncogene** is analogous to a *stuck accelerator in an automobile*; the car still moves forward even when the driver removes his foot from it.
  - An activating somatic mutation in one allele of an oncogene is generally sufficient to confer a selective growth advantage on the cell.
- **Tumor-suppressor genes** are targeted in the opposite way by genetic alterations: mutations reduce the activity of the gene product.
  - Such inactivations arise from missense mutations at residues that are essential for its activity, from mutations that result in a truncated protein, from deletions or insertions of various sizes, or from epigenetic silencing.
  - A **mutation in a tumor-suppressor gene** is analogous to a *dysfunctional brake in an automobile*; the car doesn't stop even when the driver attempts to engage it.
- A third class of cancer genes, called **stability genes** or **caretakers**, promotes tumorigenesis in a completely different way when mutated.
  - This class includes the mismatch repair (MMR), nucleotide-excision repair (NER) and base-excision repair (BER) genes responsible for repairing subtle mistakes made during normal DNA replication or induced by exposure to mutagens.
  - In the analogy to autos, **stability genes** represent the mechanics and a defective stability gene is akin to an *inept mechanic*.

Molecular Biology of Cancer



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Incorporated radionuclides.

Uneven distribution in the body and inside the cells

- There are different sites for radionuclide deposition in the body.
- Main power plant radionuclides are accumulated in the bones (strontium), and in the cellular cytoplasm (in most organs) – cesium, potassium.
- Iodine – in the thyroid gland.
- Similarity of biologic action.

The target organs of radiation damage

- ^{137}Cs is thought to be distributed equally in the body.
- But due to its similatirty to potassium it trend to accumulate in the mitochonria.
- So, in the tissues with the great energetics demand.
- Rapidly proliferating tissues – by high dose radiation.
- Heart, nervous tissue, endocrine tissue, kidney in low dose radiation.
- These organs can be damaged first.

Tropism of the radionuclides

- Bones – strontium -90
- Thyroid gland – iodine-129
- Heart, kidney, nervous tissue, endocrine glands – cesium -137.

Principal differences in the effect of external and internal radiation

Mechanisms of the damaging effect of the main dose-forming radionuclide (^{137}Cs) on organs and tissues

Mechanisms of carcinogenesis (radiation, chemical, viral)

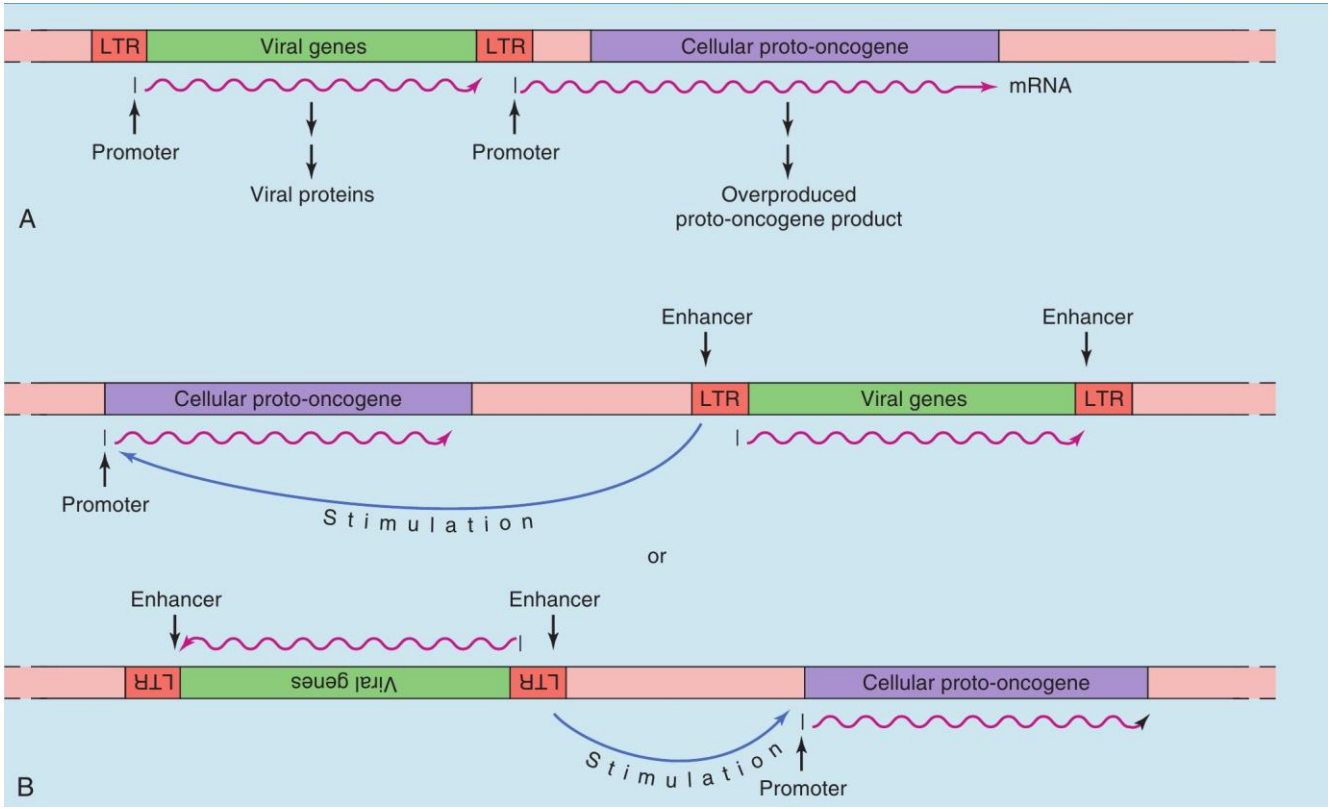
- **Carcinogenesis** (*syn. cancerogenesis, tumor growth*) – the process(es) involved in the production of cancers, including the action of carcinogens on living cells
  - *(Oxford Dictionary of Biochemistry and Molecular Biology, 2000).*
- **Carcinogenesis** – the generation of cancer from normal cells, correctly the formation of a carcinoma from epithelial cells, but often used synonymously with transformation, tumorigenesis.

Viral oncogenesis: v-oncogenes

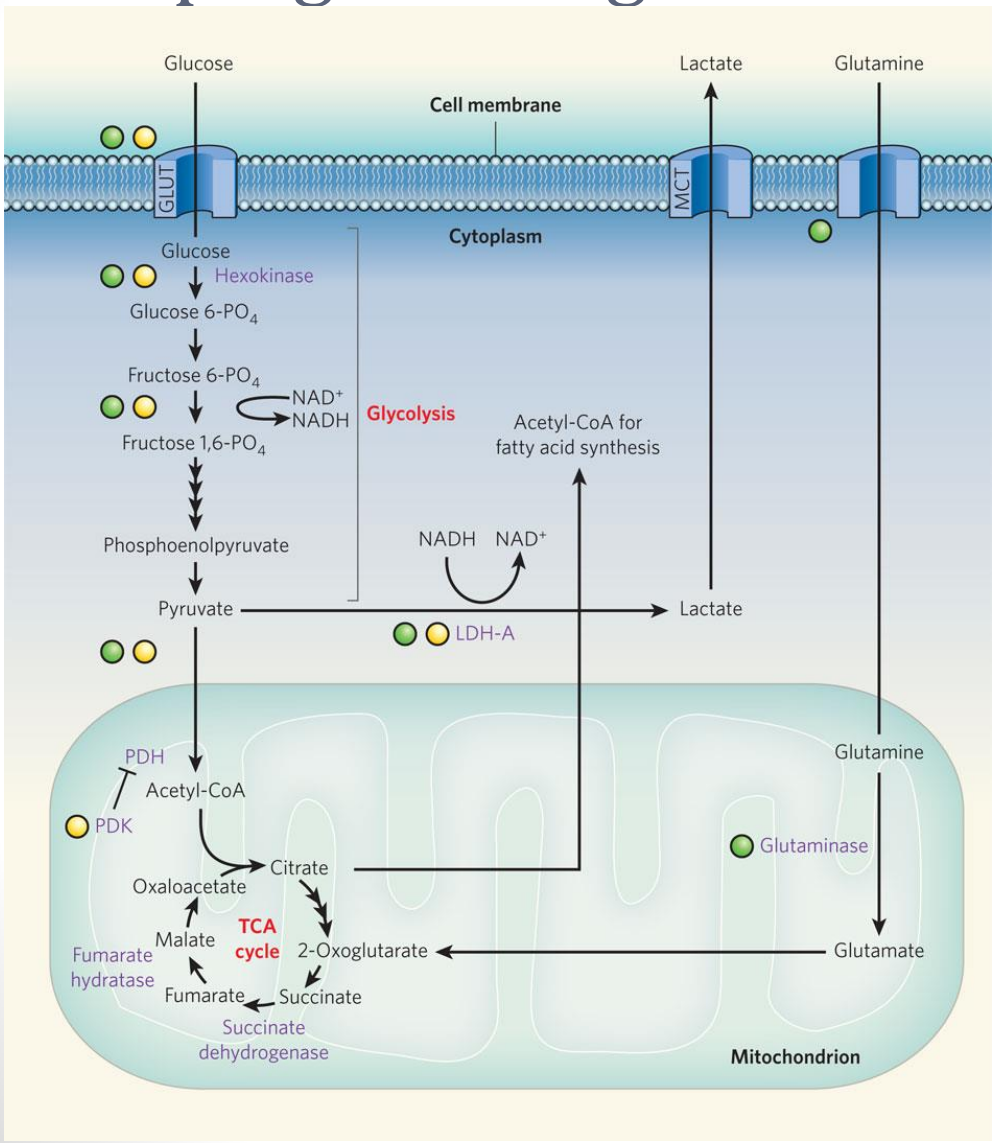
Table 19.1 Examples of Retroviral Oncogenes

Oncogene	Protein Product	Tumor (Species)
sis	Truncated version of platelet-derived growth factor (PDGF)	Simian sarcoma (monkey)
erb-B	Epidermal growth factor (EGF) receptor	Erythroblastosis (chicken)
Src	Nonreceptor tyrosine kinase	Sarcoma (chicken)
Abl	Nonreceptor tyrosine kinase	Leukemia (mouse), sarcoma (cat)
H-Ras, *K-Ras*	Ras protein (a G protein)	Sarcoma, erythroleukemia (rat)
Raf	Raf protein (a serine/threonine protein kinase)	Sarcoma (chicken, mouse)
Myc	Transcription factor of the helix-loop-helix family	Sarcoma, myelocytoma (chicken)
erb-A	Thyroid hormone receptor	Erythroblastosis (chicken)
fos, *jun*	DNA-binding proteins, components of the heterodimeric transcription factor AP 1 (activator protein 1)	Sarcoma (mouse, chicken), erythroblastosis (chicken)

Activation of protooncogene by retrovirus

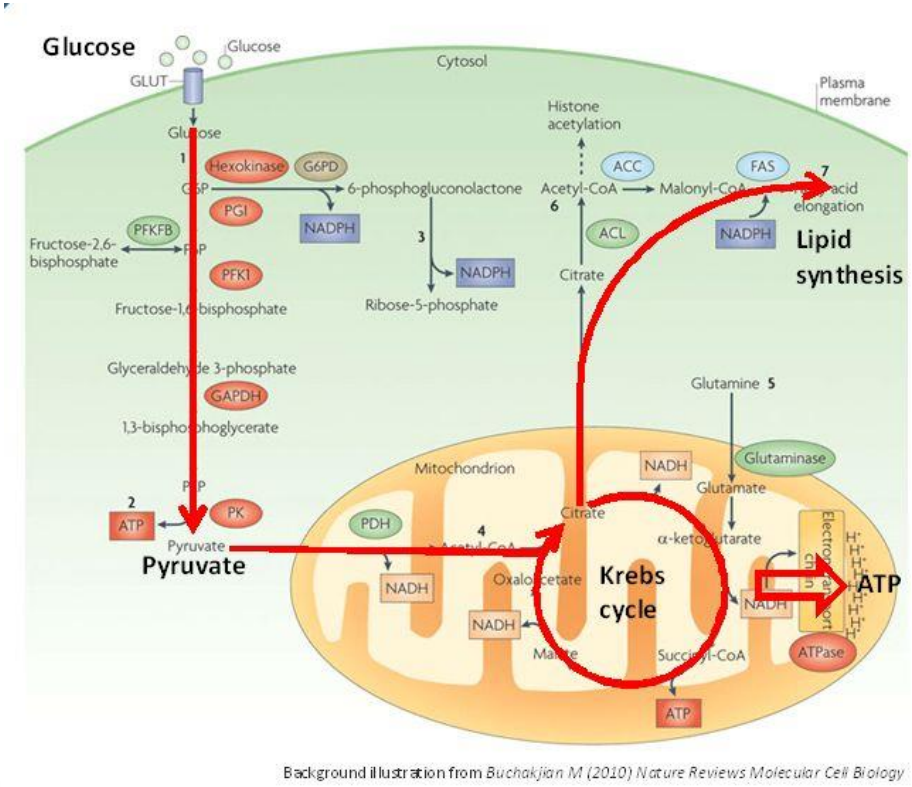


Biochemistry of carcinogenesis. Features of malignant cells metabolism. Metabolic reprogramming

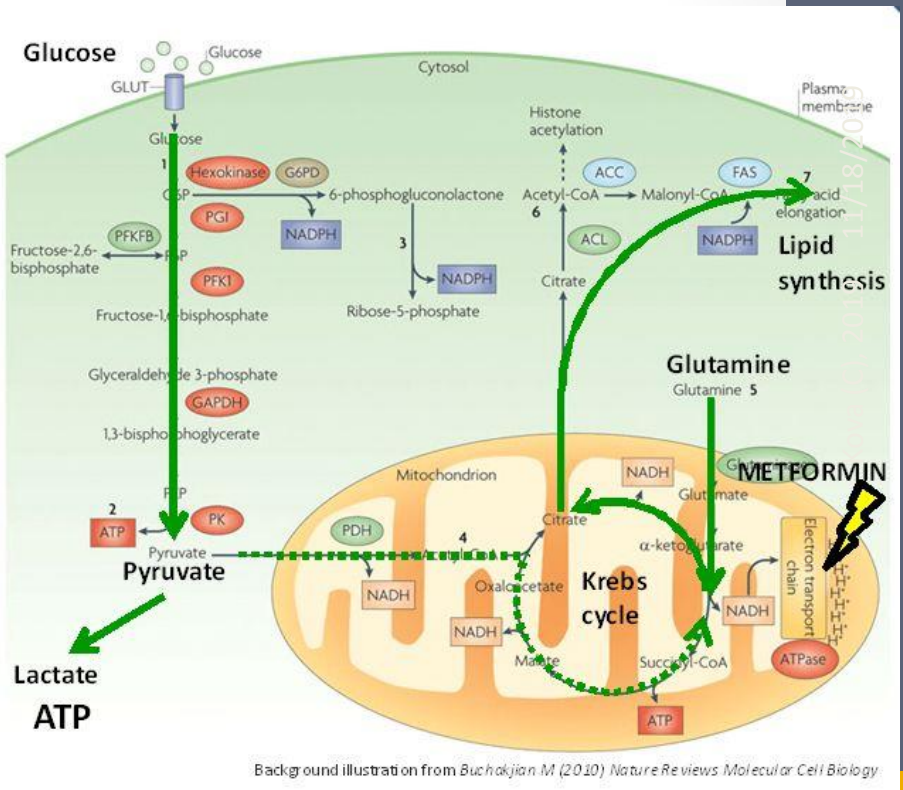


- On entering the cell, glucose is converted to pyruvate by glycolysis. In normal cells, if oxygen is available, pyruvate undergoes oxidative phosphorylation in mitochondria, through the TCA cycle. If oxygen levels are low, however, pyruvate is converted to lactate in the cytoplasm. Cancer cells drive pyruvate conversion to lactate even in the presence of oxygen. Metabolism of the nutrient glutamine is also modified in cancer. The transcription factors HIF (yellow) and MYC (green) seem to affect these metabolic pathways at various steps. For simplicity, only some chemical reactions and enzymes (purple) are shown. GLUT, glucose transporter; MCT, monocarboxylate transporter.

Metabolic reprogramming



Background illustration from *Buchakjian M (2010) Nature Reviews Molecular Cell Biology*



Background illustration from *Buchakjian M (2010) Nature Reviews Molecular Cell Biology*

Risk factors for tumor development

- age,
- genetics,
- environmental factors
  - lifestyle,
  - diet,
  - production factors,
  - iatrogenic factors,
  - diseases.
- ➔increase the risk of tumor development

To be continued