RAMA UNIVERSITY

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DEPARTMENT OF BIOTECHNOLOGY
FACULTY OF ENGINEERING & TECHNOLOGY

TOPIC

Content outline

1. Natural history of carcinogenesis
2. Target of chemical carcinogenesis

TOPIC

Physical factors

Different types of non-ionizing and ionizing radiations are majorly involved in the mechanisms of carcinogenesis.

Non-ionizing radiations are electromagnetic, with low penetration, and present a real danger for eyes and skin. This group includes ultraviolet radiation, light radiation and infrared radiation, all having the sun as the main source.

Ultraviolet B rays are mutagenic and carcinogenic, but they have a weak penetrability of only 10%, being stopped by the horny layer. They are absorbed by the ozone layer. Ultraviolet A rays penetrate the dermis easily.

Albinism and *Xerodermia pigmentosum* are hereditary factors predisposing to actinic cancer. Experimental actinic cancers are sarcoma like cancers. The main spontaneous actinic cancers in domestic animals are: vulvar melanoma in Angora goats; conjunctival squamous cell carcinoma in Hereford and Norman cattle; squamous cell carcinoma in Scottish Shepherds; squamous cell carcinoma of the external ear in white cats; squamous cell carcinoma of the external ear in sheep.

Directly ionizing radiations are electrically charged particles: negative charge, electrons, such as beta rays; positive charge, alpha particles.

•**Indirectly ionizing radiations** are particles without electric charges: photons, X rays and Gamma rays.

•The biological action of the ionizing rays depends on numerous factors: doses distributed in time add their effects, acting through summation; they can act by a single dose; their action is influenced by the presence or absence of radiosensitizing substances, such as oxygen, and radioprotective substances; the species can be more sensitive or on the contrary, resistant. For each species the following will be taken into account: the water and oxygen content; the mitotic index and the degree of tissue differentiation.

•Regarding the biological action, the major impact is at the level of the cell nucleus, chromosomes (ruptures, deletions, translocations) and DNA (thymine peroxidation, rupture of a phosphorylated bond at the level of a chain and breakage of one or two filaments). The cytoplasm is another target site, causing: arrest of metabolism after the destruction of enzymatic molecules, alteration of mitochondrial and lysosomal membranes, with the release of the enzymatic content.

•These biological actions result in either the death or the survival of the cell as carrier of a mutation.

•In human pathology, radioleukemia and radiodermitis that induce squamous cell carcinomas in radiologists are well known, as well as infant leukemia following fetal radiation, thyroid cancer after cervical radiation, etc.

•Experimental local radiation in rats causes radiodermitis evolving into sarcomas; thyroid cancer and hypophyseal tumors.

•Cancers induced by radiation are characterized by late onset, after 10 or more years, risk persisting over a period longer than 30 years.

•Repeated low intensity traumas can determine metaplastic, dysplastic changes, and even tumor proliferation. The involvement of traumas in the development of tumors should be regarded with circumspection, since exophytic tumors are submitted to the action of traumatic factors that cause erosions and ulcers.

•Osteomas occurring at the level of bones on which repeated traumas are exerted are well known in animals.

Principle of carcinogenesis by UV radiation

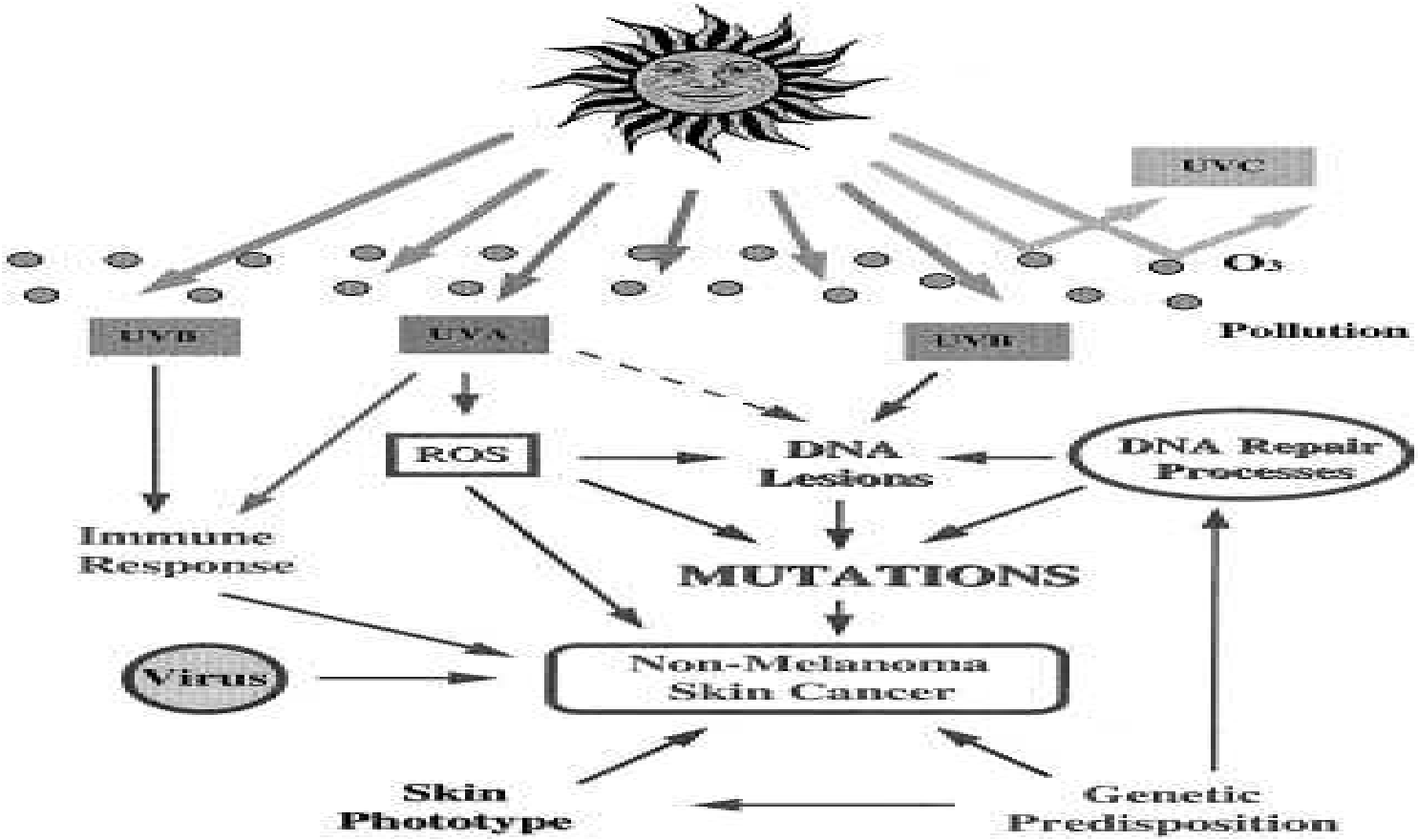
•The incidence of human skin cancers collectively outnumbers that of all other cancers combined. Ultraviolet radiation (UVR) has long been understood to produce photoproducts in DNA, some of which give rise to specific somatic mutations capable of driving epithelial and melanocytic cancers.

• Accordingly, the vast numbers of somatic point mutations found in melanoma and basal and squamous cell carcinoma are predominantly base changes associated with UVR. While *TP53* and *NOTCH1* mutation have emerged as hallmarks of squamous cell carcinomas, as have *PTCH* mutations in basal cell carcinoma, large-scale sequencing projects are illuminating dozens of other known tumor suppressors and oncogenes mutated at low frequency in both melanomas and nonmelanoma skin cancer.

• Thus, cells tolerating DNA damage without triggering apoptosis eventually acquire mutations favoring clonal growth, and these populations in turn accumulate additional, lower frequency mutations enhancing oncogenic cell behavior.

•The process of UV-driven transformation in skin cancers is markedly accelerated not only by deficiencies in DNA repair, but also by immunodeficiency, suggesting that surveillance mechanisms actively eliminate UV-damaged cells, perhaps through T-cell detection of neoepitopes.

•Genetic factors modulating risk of UV carcinogenesis include resistance conferred by melanin and susceptibility associated with impaired free-radical clearance. Epidemiological efforts have begun validating systemic chemopreventatives, such as caffeine, which may be deployed, in concert with sun protection and avoidance, to further delay UV carcinogenesis.



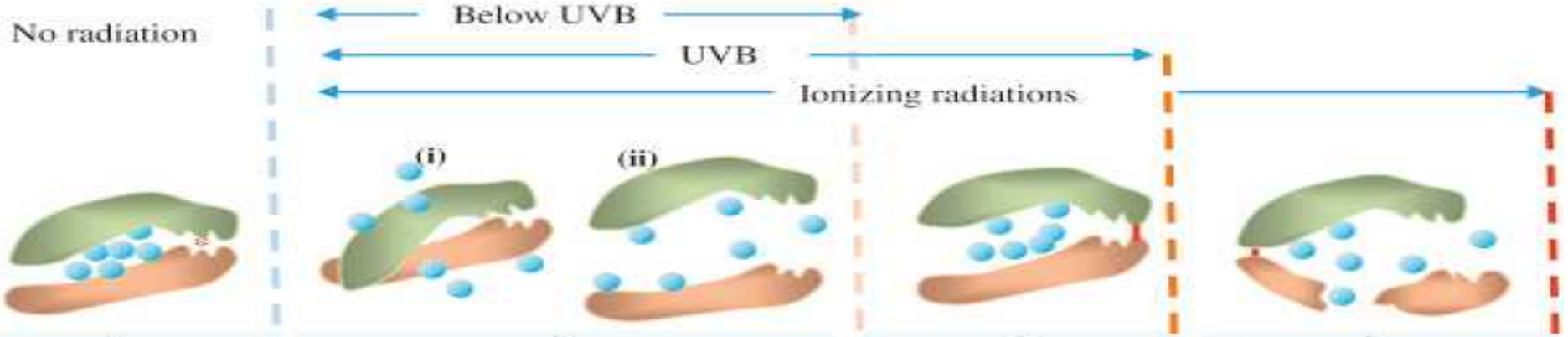
A. Atomic (oxygen atom with vacant vertical *2p* orbitalin resting state)

A
Radiations $>10^{-7}$m wavelength only increase atomic movement, i.e., heat.

B
Radiations $<10^{-7}$m wavelength also move electrons to higher energy orbital (in this diagram, 2s →2p)

C
Radiations $<10^{-9}$m wavelength also eject electrons from highest energy shell, i.e., ionization. (It is thought that at least eight photons striking simultaneously may be necessary.)

B. Molecular and inter-molecular results leading to reductions in function



A
Normal molecular complex with enzymic site (•).

B
Heat may cause (i) loss of water which may lead to aggregation. Heat in other macromolecules may also cause (ii) disruption of non-covalent bonds and dissociation.

C
Excitation of electrons may cause altered non-covalent bonds and new covalent bonds (↑).

D
Ionization may cause breaks of covalent bonds and new covalent bonds (↑).

C. Effects in local tissues, and in the rest of the body

Heat, UV, and ionizing radiations are themselves inflammogenic. Also denatured fragments of macromolecules in tissues are inflammogenic. When denatured fragments produced by almost any mechanism enter the blood circulation they cause systemic effects such as fever and malaise.

References & Recommended reading

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Recommended reading

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