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A Review on UV-Induced DNA Damage and the Pathophysiology of Impacted Gene Skin Cancer

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ABSTRACT; It has become possible to test mammalian cells' ability to repair DNA using UV-damaged viruses and gens. The non-replicating recombinant adenovirus Ad5HCMV space, specifically, has been utilized to investigate the constitutive and inducible repair of UV-damaged DNA in human cells. It expresses the B-galactosidase reporter gene. Normal human fibroblasts with low UV fluences were previously exposed to UV light, which temporarily enhanced host cell reactivation for the production of the UV-damaged reporter gene[1].

Introduction: The Skin is our body's largest and most versatile organ. Adult human skin has an average surface area of 20 square feet[2)]. As a dynamic interface between our body and its environment, the skin provides many distinct functions[3]. It serves as a protective barrier preventing internal tissues from exposure to trauma ultraviolet radiation, temperature extremes, toxins, and bacteria[4]. Other important functions include sensory perception, immunologic surveillance, thermoregulation, and control of fluid loss[5].

Aging skin: The number and proportion of older skin people are increasing worldwide at an unprecedented rate, and recent U.S CB statistics detail an ever-increasing American life expectancy[6]. The incidence of skin cancer increases exponentially with age. Potentially fatal skin malignancies, such as melanoma and cutaneous T-cell lymphoma, as well as numerous skin conditions that rarely threaten life but compromise its quality, are dramatically increasing in the geriatric population[7,8].

Keywords:DNA,SkinCa,UV, antioxidants

I. PATHOPHYSIOLOGY

Cellular senescence: It seems that the primary causative factor behind the onset of skin cancer in the human population is solar UV radiation[9]. It is commonly known that UVB and UVA radiation primarily affect cellular DNA through photosensitized reactions and direct effects, respectively[10]. For years, the absence of precise and quantitative measurement techniques has hindered the precise evaluation of the end products of these photoreactions. This is especially relevant to the individual determination of dimeric pyrimidine photoproducts, such as pyrimidine (6-4) pyrimidonephotoadducts (6-4PPs), cis-syn cyclobutadipyrimidines (CPDs), and related valence Dewar isomers (DewarPPs), for which, until recently, there was a paucity of information[11]. However, relevant data on the distribution and repair of the three latter classes of photoproducts within the DNA of plasmids, isolated cells, and tissues were gained mostly from serological approaches. These include ELISA, RIA, and immuno-dot-blot measurements, together with immunostaining detection through the availability of monoclonal and polyclonal antibodies. We may also mention the recent development of an immunological method aimed at measuring CPDs and 6-4PPs in the DNA of isolated cells in association with the

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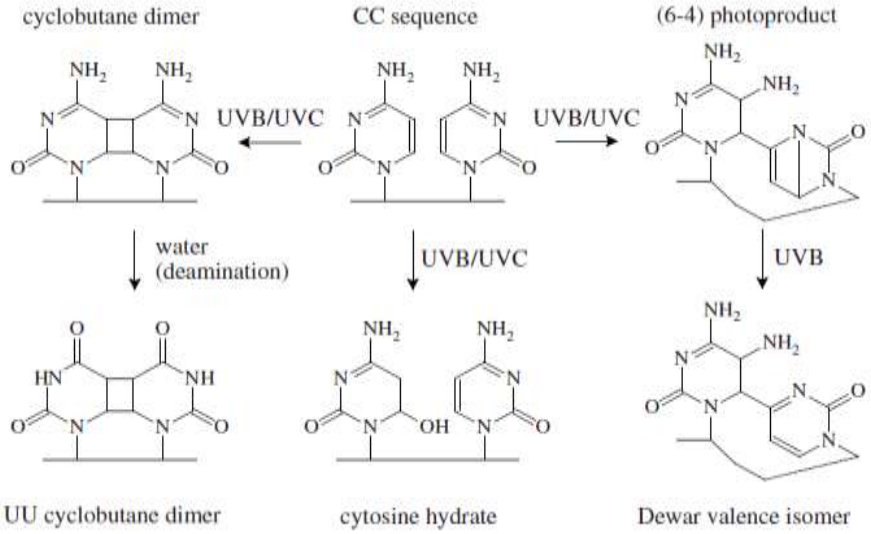

Figure 1Chemical structure of the main UVB-induced monomeric and dimeric cytosine photoproducts. An example of a secondary deamination reaction that may affect 5,6- dihydrocytosine residues is provided for the cyclobutane dimer.

Mammalian cells can undergo only a limited number of cell divisions and then arrive irreversibly in a state known as replicative senescence[12], after which they are refractory to mitogenic stimuli. This fact has led to the perception that aging evolved in multicellular organisms as a cancer prevention mechanism since it prevents the unlimited and possibly unregulated growth of cells whose DNA has been progressively damaged over their organism's lifespan[13].

The free radical theory of aging and oxidative stress "A causative role for reactive oxygen species (ROS) in aging processes, referred to as the free radical theory of aging, proposes that ROS in biological systems causes a decline of organ systems that eventually leads to death[14].

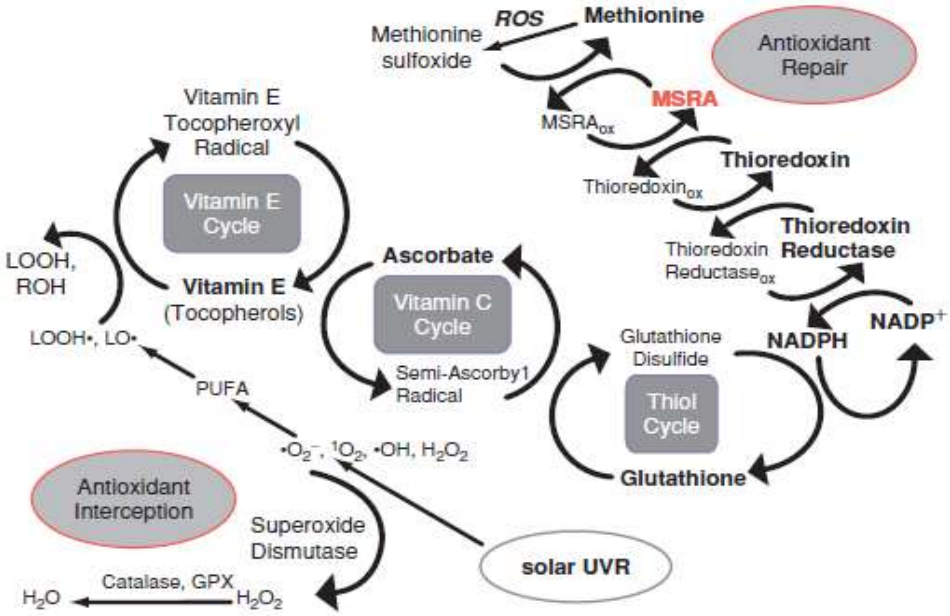

Figure 2The antioxidant network of the skin and free radical interception.

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Evidence for inducible DNA repair

The enhanced capacity of mammalian cells to repair DNA following exposure to carcinogens, the p53-mediated enhancement of NER by the DNA damaged-induced GADD45 gene, and the identification of a novel DNA repair response triggered by irradiation of cells at the G1/S border are just a few of the studies that have added more evidence for damage-induced DNA repair pathways in mammalian cells. Pretreatment of normal human lung fibroblasts with the medicine emodin enhances NER of UV and cisplatin-damaged DNA; pretreatment of cells with dinucleotides before UV irradiation increased the repair of UV-induced DNA damage as determined by unscheduled DNA synthesis[15]. Pretreatment of normal human fibroblasts with low doses of quinacrine mustard resulted in an enhanced rate of removal of CPD by NER, also giving evidence for an inducible NER response in human cells. Although most of these studies[16].

Nucleotide excision repair

DNA is susceptible to damage induced by various endogenous and exogenous agents. The genome's integrity is maintained mainly by several highly conserved DNA repair pathways. Nucleotide excision repair (NER) is the best characterized of these DNA repair pathways[17]. NER is required to remove diverse helix-distorting DNA adducts, including those induced by ultraviolet (UV) light. Several distinct steps of NER have been elucidated, and many recent reviews have dealt with this topic in detail. In a word, the DNA lesion needs to be acknowledged, and the damaged area needs to have the repair equipment brought in. Subsequently, the broken DNA strand is cut twice. One is 20–22 to the 50 side of the lesion, and the other is 5–7 to the 30 side[18]. The oligonucleotide of approximately 30 nucleotides containing the damaged bases is displaced, leaving a single-stranded gap. Subsequently, a nascent strand is synthesized to replace the displaced oligonucleotide. Lastly, the 30 end of the nascent DNA is ligated to existing DNA to make a continuous DNA strand. In this way, cells can remove a wide range of bulky intrastrain DNA adducts[19]. NER can be further subdivided into two interrelated sub-pathways differing in NER's initial lesion recognition stage. The repair of UV-induced DNA damage occurs more rapidly in the transcribed strands of active genes than in the remainder of the genome. This specialization of NER is thought to involve a mechanism that directly couples RNA polymerase II transcription to NER, and this has been termed transcription-coupled nucleotide excision repair (TCNER)[20]. Lesions induced

II. DISCUSSION & CONCLUSION:

by UV light blocks the progression of RNA polymerase II, preventing the expression of polyadenylated RNAs[21]. TCNER removes the impeding lesions and thus permits the rapid resumption of mRNA synthesis following UV irradiation. UV dimers located elsewhere in the genome are repaired by the global genomic repair (GGNER) sub-pathway of NER, and these lesions have almost no impact on the recovery of transcription following UV irradiation. Thus, two overlapping sub-pathways of NER have evolved to deal with lesions with distinct biological implications[21].

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