Journal of Cardiovascular Disease Research

ISSN: 0975-3583, 0976-2833 VOL12, ISSUE 05, 2021

EXPLORING UV-INDUCED DNA DAMAGE AND ITS ROLE IN SKIN CANCER PATHOPHYSIOLOGY

NIRANJAN BABU MUDDULURU*, PRABHU SETTY K

Department of Pharmacognosy, Seven Hills College of Pharmacy, Tirupati, A.P., India

Corresponding Author
Dr. M. Niranjan Babu
Professor
Department of Pharmacognosy
Seven Hills College of Pharmacy,
Tirupati, A.P., India – 517561
Contact: 7702484513
Email: principal.cq@jntua.ac.in

ABSTRACT:

Testing mammalian cells' capacity to repair UV-damaged DNA has been made feasible using UV-damaged viruses and genes. The non-replicating recombinant adenovirus Ad5HCMV space, specifically, has been employed to study constitutive and inducible repair mechanisms of UV-damaged DNA in human cells, utilizing the B-galactosidase reporter gene. Human fibroblasts exposed to low UV fluences were previously treated with UV light, temporarily enhancing host cell reactivation to produce the UV-damaged reporter gene.

INTRODUCTION:

The skin, our body's largest and most adaptable organ, covers an average surface area of 20 square feet in adults. Serving as a dynamic interface between the body and its environment, the skin plays vital roles such as providing a protective barrier against trauma, ultraviolet radiation, temperature extremes, toxins, and bacteria. It also contributes to sensory perception, immunological surveillance, thermoregulation, and maintenance of fluid balance.

Aging Skin:

The global population of elderly individuals is growing rapidly, leading to an increasing prevalence of age-related skin issues. Statistics from the U.S. Census Bureau indicate a rising life expectancy among Americans. With advancing age, the incidence of skin cancer, including potentially fatal types like melanoma and cutaneous T-cell lymphoma, rises significantly. Additionally, numerous non-life-threatening skin conditions compromise the quality of life for older adults.

Keywords: DNA, SkinCa, UV, antioxidants

PATHOPHYSIOLOGY

Cellular Senescence: Solar UV radiation is considered the primary causative factor for skin cancer in humans. UVB and UVA radiation impact cellular DNA through photosensitized reactions and direct effects, respectively. The precise evaluation of the end products of these photoreactions has historically been challenging due to the lack of precise measurement techniques. Specifically, dimeric pyrimidine photoproducts such as pyrimidine (6-4) pyrimidone photoadducts (6-4PPs), cis-syn cyclobutadipyrimidines (CPDs), and related valence Dewar isomers (DewarPPs) have lacked comprehensive data until recently. Progress in understanding these photoproducts has been facilitated by serological approaches including ELISA, RIA, immuno-dot-blot assays, and immunostaining using monoclonal and polyclonal

ISSN: 0975-3583, 0976-2833 VOL12, ISSUE 05, 2021

antibodies. Recent advancements have led to the development of immunological methods aimed at quantifying CPDs and 6-4PPs in isolated cell DNA, enhancing our understanding of their distribution and repair mechanisms.

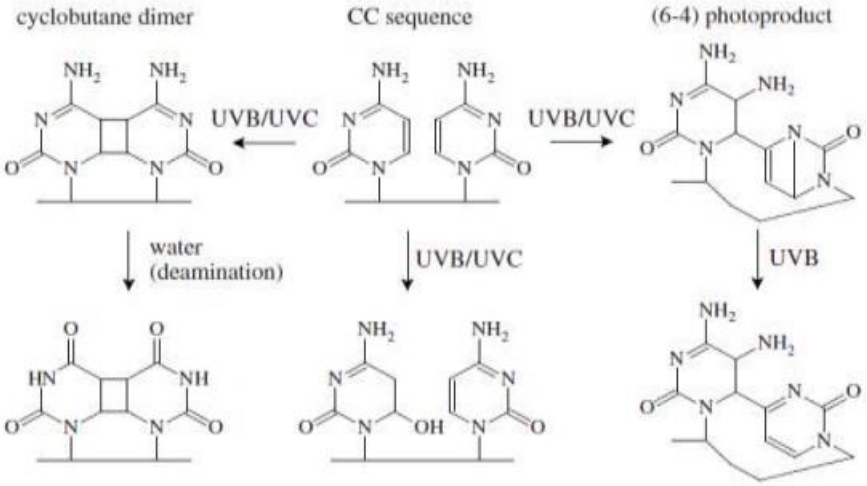

Figure 1Chemical structure of the main UVB-induced monomeric and dimeric cytosine photoproducts. An example of a secondary deamination reaction that may affect 5,6-dihydrocytosine residues is provided for the cyclobutane dimer.

Mammalian cells have a finite capacity for division, entering an irreversible state called replicative senescence after a limited number of divisions. In this state, cells become unresponsive to mitogenic signals. This phenomenon suggests that aging may have evolved in multicellular organisms as a mechanism to prevent the uncontrolled growth of cells with progressively damaged DNA over the organism's lifespan.

The free radical theory of aging and oxidative stress posits that reactive oxygen species (ROS) play a causative role in aging processes. This theory suggests that ROS cause a decline in organ systems, ultimately leading to death.

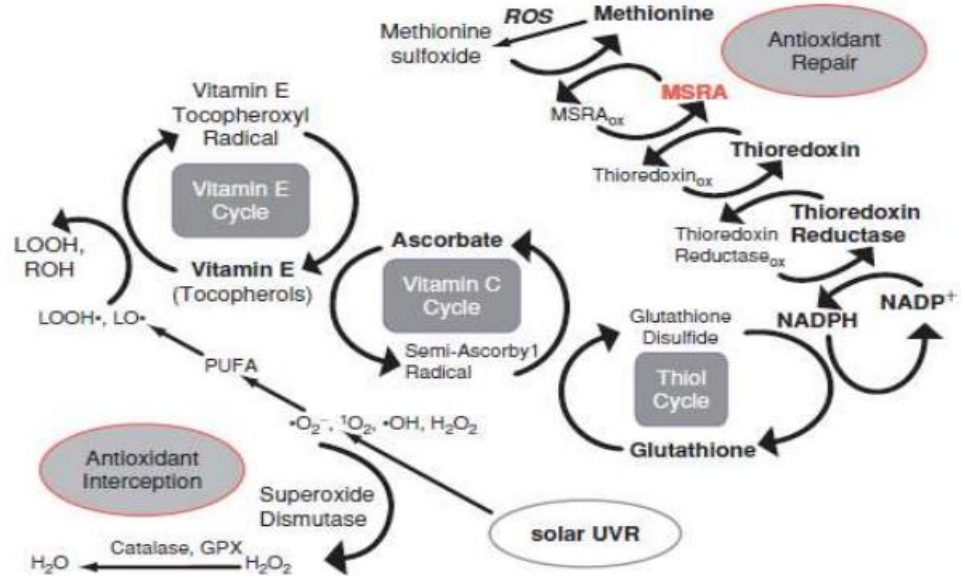

Figure 2The antioxidant network of the skin and free radical interception

Evidence supporting inducible DNA repair pathways in mammalian cells has been bolstered by several studies. For instance, studies have shown that mammalian cells can enhance their ability to repair DNA following exposure to carcinogens. This includes mechanisms such as p53-mediated enhancement of nucleotide excision repair (NER) through the GADD45 gene

ISSN: 0975-3583, 0976-2833 VOL12, ISSUE 05, 2021

induced by DNA damage. Additionally, novel DNA repair responses have been identified, particularly triggered by irradiation of cells at the G1/S border.

Research has demonstrated that pretreatment of normal human lung fibroblasts with emodin can enhance NER of UV and cisplatin-damaged DNA. Similarly, pretreatment with dinucleotides prior to UV irradiation has been shown to increase repair of UV-induced DNA damage, as assessed by unscheduled DNA synthesis. Moreover, pretreatment with low doses of quinacrine mustard enhances the removal of cyclobutane pyrimidine dimers (CPDs) through NER in human fibroblasts, providing further evidence for an inducible NER response in human cells.

NER is a well-characterized DNA repair pathway crucial for maintaining genomic integrity. It functions by recognizing and removing helix-distorting DNA adducts induced by various agents, including UV light. The process involves sequential steps: recognition of the DNA lesion, excision of the damaged DNA strand flanked by specific cuts, synthesis of a new strand to replace the excised segment, and ligation to ensure continuity of the DNA strand.

Furthermore, NER can be subdivided into two interrelated sub-pathways, differing primarily in how they recognize initial lesions. Notably, NER operates more efficiently on transcribed strands of actively transcribing genes, a process known as transcription-coupled nucleotide excision repair (TCNER). This specialization likely involves a mechanism that directly links RNA polymerase II transcription to NER, facilitating prompt repair of lesions within active genes compared to the rest of the genome.

DISCUSSION & CONCLUSION

UV light induces lesions in DNA that can block RNA polymerase II, thereby inhibiting the expression of polyadenylated RNAs. This blockage is effectively managed by transcription-coupled nucleotide excision repair (TCNER), which specifically removes the lesions and allows rapid resumption of mRNA synthesis after UV irradiation. In contrast, UV-induced dimers located elsewhere in the genome are repaired by the global genomic repair (GGNER) sub-pathway of nucleotide excision repair (NER). These lesions have minimal impact on transcription recovery post-UV irradiation.

Thus, mammalian cells have evolved two overlapping sub-pathways of NER to address DNA lesions with distinct biological consequences. TCNER ensures swift repair of lesions within actively transcribing genes, crucial for maintaining gene expression integrity, while GGNER handles lesions in non-transcribed regions, preserving genome stability overall. This specialized repair mechanism highlights the cellular strategies to mitigate the detrimental effects of UV-induced DNA damage on transcription and genomic integrity.

REFERENCE:

1. M.Wakasugi,etal.(2002).DDB accumulates at DNA damage sites immediately after UV irradiation and directly stimulates nucleotide excision repair. J. Biol. Chem., 277, 1637–1640.
2. D.M.Tolbert,G.J. Kantor (2014). Definition of a DNA repair domain in the genomic region containing the human p53 ene. Cancer Res, 56, 3324–3330.
3. M.S.Tang,V.A. Bohr, X.S. Zhang, J. Pierce, P.C.Hanawalt(2013).Quantificationof aminofluorene adduct formation and repair in defined DNA sequences in mammalian cells using the UvrABC nuclease.J. Biol.Chem., 264, 14455–14462.
4. R.Drouin,J.P.Therrien,M.Angers,S. Ouellette (2008). In: T. Moss (Ed.). Methods in molecular biology:DNAProtein Interactions, Principles,and Protocols (pp. 175–219) Humana Press, Totowa, N.J.
5. M.Scheffner,B.A.Werness,J.M. Huibregtse,A.J. Levine, P.M. Howley (2019). The E6 oncoprotein encoded by human papillomavirus types 16 and 18 promotes the degradation of p53. Cell, 63, 1129–1136.

ISSN: 0975-3583, 0976-2833 VOL12, ISSUE 05, 2021

6. T.D. Kessis, R.J. Slebos, W.G. Nelson, M.B. Kastan, B.S. Plunkett, S.M. Han, A.T. Lorincz, L. Hedrick, K.R. Cho (2016). Human papillomavirus 16 E6 expression disrupts the p53-mediated cellular response to DNA damage. Proc. Natl. Acad. Sci., 90, 3988–3992.
7. W. Liu, et al. (2018). Nuclear transport of human DDB protein induced by ultraviolet light. J. Biol. Chem., 275, 21429–21434.
8. J.Gannon,D. Lane (2017). Protein synthesis required to anchor a mutant p53 protein which is temperature-sensitive for nuclear transport. Nature, 349, 802–806.
9. G. Li, V.C. Ho, D.L. Mitchell, M.J. Trotter, V.A. Tron (2013). DifferentiationDependent P53 Regulation of Nucleotide Excision Repair in Keratinocytes. Am. J. Pathol., 150, 1457–1464.
10. D.Michalovitz, O.Halevy, M. Oren (2016).Conditional inhibition of transformation and of cell proliferation by a temperature-sensitive mutant of p53. Cell, 62, 671–680.