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DNA REPAIR ENZYMES AS THERAPEUTIC AGENTS: A REVIEW

DNA damage is a long-recognized factor for the development and progression of cancer in humans. Genome instability is the leading factor behind the development of cancer. There are some DNA repair pathways and DNA damage checkpoints in all creatures, without which the functional stability gets compromised. Impaired DNA results in genomic instability leading to the development of cancer, limited lifespan, and early aging. UV rays and ionizing radiation are the major exogenous factors responsible for DNA damage, causing lesions in DNA that lead to photoaging. Protection administered by conventional sunscreens is merely prophylactic and does not work if lesions have already occurred. There is an increasing demand for such a product can reverse or delay the effects of photoaging thus the protection offered by conventional sunscreens can be improved. This review focuses on recent developments on the involvement of various DNA repair enzymes in the treatment of cancer as well as in skincare products such as a sunscreen.

Keywords: *DNA damage, genome instability, DNA repair pathways, cancer, photoaging, sunscreen.*

Preservation of genetic information is essential for the continuance of life but mutagenesis plays a crucial part in its maintenance and evolution. Though mutagenesis is considered essential for providing survival value, it sometimes becomes troublesome especially when it contributes to cancer, aging, and many other diseases [1]. DNA is the basis of the existence of many organisms, it is a highly reactive molecule and quite susceptible to chemical alterations resulting from internal and external sources.

Activation of DNA checkpoint pathways is indispensable for DNA repair mechanisms. For different forms of DNA damage, there are different repair pathways. Major pathways are mismatch repair, base excision repair, nucleotide

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excision repair, homologous recombinational repair, and non-homologous joining [2].

Genome stability plays a major role in subduing cancer formation. Exposure to UV results in DNA damage; it disturbs genomic stability leading to mutations that cause precancer or cancer in later stages of life. Both intrinsic and extrinsic factors are responsible for aging in humans, the former are characterized by gradual loss of tissue elasticity [3]. Exposure to extrinsic or environmental factors results in premature aging or photoaging. Sunscreen prevents photoaging by occluding the transfer of UV-R but does not repair the already occurred damage. However, there are some sunscreens that contain SPF along with several DNA repair enzymes and antioxidants. They are capable of protecting as well as repairing damages caused by UV-R unlike conventional sunscreens [4, 5].

DNA Damage. DNA is the basis of the existence of many organisms. It is a highly reactive molecule quite susceptible to chemical alterations resulting from internal and external sources [1]. Changes in nucleotide sequence and expression of defective proteins result in abnormal cellular functions. DNA damage leads to apoptosis, senescence, and instability of the genome affecting the development and aging of organisms [6—8]. There are two classes of DNA damaging agents: clastogens and aneugens [9, 10]. Aneugens cause genomic instability with numerical aberrations of chromosomes via DNA replication stresses. Clastogens cause structural aberrations of chromosomes, which potentially trigger mutations via repairing errors [11, 12].

Endogenous DNA damage. Certain endogenous agents are responsible for induction of replicative stress which leads to generation of free radicals and reactive oxygen species (ROS). Replication errors, DNA base mismatches, Topopisomerase DNA complexes, spontaneous base deamination, abasic sites, oxidative DNA damage, and DNA methylation are possible causes of endogenous DNA damage [1].

Exogenous DNA damage. DNA damage is also induced by physical and chemical agents such as ionizing radiation, UV radiation, alkylating agents, aromatic amines, polycyclic aromatic hydrocarbons, toxins, reactive electrophiles, and environmental stresses such as extreme temperature and oxidation conditions [13, 14].

DNA Repair Mechanisms. Activation of DNA checkpoint pathways is indispensable for DNA repair mechanisms (Table 1). For different forms of DNA damage, there are different repair pathways [15].

DNA Repair Enzymes. In 2015 three scientists Tomas Lindahl, Paul Modrich, and Aziz Sancar were awarded Nobel Prize in Chemistry

Table 1. **DNA Repair mechanisms for different types of DNA lesions**

Repair Mechanism	Lesion Feature	Genotoxic Source
Base excision repair (BER)	Oxidative lesions	Reactive oxygen species (ROS)
Nucleotide excision repair (NER)	Helix-distorting lesions	UV radiation
Translesion synthesis	Various lesions	Various sources
Mismatch repair (MR)	Replication errors	Replication
Single strand break repair (SSBR)	Single strand breaks	Ionizing radiations, ROS
Homologous recombination (HR)	Double strand breaks	Ionizing radiations, ROS
Non-homologous end joining (NHEJ)	Double strand breaks	Ionizing radiations, ROS
DNA interstrand crosslink repair pathway	Interstrand crosslinks	Chemotherapy

Source: Ciccia and Elledge, 2010.

for their mechanistic study of DNA repair. The Nobel was awarded "For mechanistic studies of DNA repair". Mr. Lindahl is from the Francis Crick Institute. "He demonstrated that DNA decays at a rate that ought to have made the development of life on Earth impossible. This insight led him to discover a molecular machinery, base excision repair, which constantly counteracts the collapse of our DNA," reported the press release. Mr. Modrich is from the Howard Hughes Medical Institute and Duke University School of Medicine. "He demonstrated how the cell corrects errors that occur when DNA is replicated during cell division. This mechanism, mismatch repair, reduces the error frequency during DNA replication by about thousand-fold". Mr. Sancar is from the University of North Carolina. "He has mapped nucleotide excision repair, the mechanism that *cells use* to repair UV damage to DNA. People born with defects in this repair stem will develop skin cancer if they are exposed to sunlight. The cell also utilizes nucleotide excision repair to correct defects caused by mutagenic substances, among other things." In 1978 Tanaka demonstrated that bacterial DNA repair enzymes can function inside human cells [16].

Ligases. Discovered in 1967 by Gellert, Lehman, Richardson, and Hurwitz Laboratories [17], ligases have become extremely useful tools in molecular biology. DNA ligases keep the integrity of the DNA duplex phosphodiester backbone. DNA ligases in humans are encoded by L1G1, L1G3 & L1G4 genes. The enzymes have catalytic regions, flanked by the distinct N and C-terminal regions. DNA ligase plays a major role in almost all repair pathways, which makes it a favorable target for the fabrication of inhibitors that can regulate the action of genotoxic regulators used in the treatment of cancer. All DNA repair events require DNA joining;0 three genes encoding DNA ligases are present in humans for the purpose of repair and replication. Cellular functions of human DNA ligase include nuclear DNA replication, mitochondrial DNA replication and repair, nuclear DNA excision repair, nuclear SSB repair, and nuclear DSB repair [18—20].

T4 Bacteriophage Endonuclease V (T4 Endonuclease V). T4 Endonuclease V was isolated from *Escherichia coli* infected with T4 bacteriophage. This enzyme can recognize CPD and uses glycosylase and AP lyase to repair damaged DNA. The process involves two reactions catalyzed by enzymes glycosylases and AP lyase. The former uses glycosylase and results in the formation of apurinic site and release of thymine. AP lyase at the site of the missing base breaks the phosphodiester backbone, thus causing a single-stranded break. The bases around this site are removed by exonuclease supplied by host cells. The gap thus created is filled by polymerase, and the damaged DNA gets repaired [21]. With T4 treatment, induction of Matrix Metalloproteinases-1 can be reduced resulting in reduced collagen deterioration [22].

Photolyase. Photolyase belongs to the class of flavoproteins, which contains FAD (Flavin Adenine Dinucleotide) as a cofactor [23]. UV-induced DNA damage of cyclobutane pyrimidine dimer, and a pyrimidine-pyrimidone photoproduct is repaired by this enzyme where FAD acts as a catalytic factor. The enzyme recognizes the lesions caused by thymine dimers which gets repaired via direct absorption of blue light by FAD molecules. Overexpression of MMP-1(Metalloproteinase-1) is responsible for photoaging as it destroys the collagen present in human skin cells. Photolyase effectively reduces the expression of MMP-1 in dermal compartments resulting in cell regeneration and inhibition of UV-induced apoptosis. It also inhibits cytokine IL-6 [24]. Photolyases are of two types: CPD (Cyclobutane Pyrimidine Dimer) photolyase and (6—4) photolyase. Both photolyases are capable of reappearing different photoproducts namely CPD & PPD (pyrimidine-pyrimidone photoproduct). CPDs

are more mutagenic as compared to PPDs [25]. Conventional sunscreen along with CPD photolyase has been proved to be far more effective in reducing DNA and apoptosis caused by UV-B radiation [26].

UV Endonucleases. UV Endonucleases are isolated from *Micrococcus luteus*. They are known to stimulate the ER (Excision Repair) process in Mammalian cells [27] and to reduce CPD by 18% in the case of UV-irradiation of healthy people [28].

DNA Repair Enzymes: Role in Cancer Treatment. Genome stability performs a major role in subduing cancer formation. Exposure to UV results in DNA damage, it disturbs genomic stability leading to mutations that cause pre-cancer or cancer in later stages of life. UV exposure results in i) activation of p53 gene: its elevated expression results in cell death from apoptosis in cells with damaged DNA [29]; ii) increased MMP1 induction: it is responsible for photoaging [24]; iii) activation of c-FOS: it is a proto-oncogene [30].

DNA ligase inhibitors serve as potential cancer therapeutics. Non-Homologous End Joining is considered a therapeutic target in certain cancers, and expression levels of DNA ligase IIIα and DNA ligase VI can be used as biomarkers to identify cancers with abnormal repair of DSBs by Non-Homologous End Joining [31].

DNA Repair Enzymes: Role in Skincare. Both intrinsic and extrinsic factors are responsible for aging in humans, the former are characterized by gradual loss of tissue elasticity. Exposure to extrinsic or environmental factors results in premature aging or photoaging [3]. Photoaging refers to alterations in functional, clinical, and histological attributes, which develop gradually in the case of UV-exposed skin [32]. Photoaging results in wrinkles, leathery skin, pigmentation, impaired wound healing, and loss of repair and regeneration potential of skin [33, 34]. DNA damage is the leading cause of photoaging. With chronic UV exposure, DNA repair mechanisms fail to repair the persistent DNA damage, which may cause skin cancer development and photoaging [35].

There is a significant rise in UV-R due to the continued depletion of the ozone layer in the stratosphere, which leads to chronic exposure. Continued exposure to extrinsic and unnatural UV-R has increased the demand for non-homologous mechanisms that can reverse or delay the effects of photoaging, thus the protection offered by conventional sunscreens can be improved. Today this protection is merely prophylactic and becomes bootless if lesions have already occurred [5].

UV-induced ROSs are notoriously responsible for photoaging in humans. They affect dermal fibroblasts via cytoplasmic signal transduction pathway. These cells are responsible for growth, differentiation, and connective tissue deterioration. ROS species are capable of causing permanent alterations in gene expression pathways related to collagen deterioration. This type of damage is repaired by Base Excision Repair System [36].

Sunscreens prevent against photoaging by occluding the transfer of UV-R but they do not repair already occurred damages, which renders them useless in the case of UV exposed skin. But there are some sunscreens that contain SPF along with several DNA repair enzymes and antioxidants. They are capable of both protecting and repairing damages caused by UV-R unlike conventional sunscreens [4, 5].

T4 Endonuclease V and DNA photolyase are DNA repair enzymes that can effectively remove damaged DNA fragments from any cell. T4 Endonuclease V was isolated from *Escherichia coli* infected with T4 bacteriophage. This enzyme stimulates skin repair, regeneration, and reconstruction thus effectively preventing photoaging [37]. Photolyase belongs to the class of flavoproteins which repair cyclobutane pyrimidine dimer and pyrimidine-pyrimidone photoproduct using blue light [38].

Table 2. **Review of sunscreens containing DNA repair enzymes**

Brand Name	Country	SPF	DNA Repair
Ateia®	Kwizda Pharma GmbH, Vienna, Austria	50+ 50 30 25	Liposome-encapsulated photolyase, Endonuclease
Aryfotona® AK-NMSC	Isdin, SA, Barcelona, Spain	100+	Liposome-encapsulated photolyase
Heliocare 360 AK Fluid	Cantabria Labs, Madrid, Spain	100+	Liposome-encapsulated photolyase, Endonuclease, 8-Oxoguanine glycosylase
Ladival® Med	STADA Arzneimittel, Bad Vilbel, Germany	20 15	Liposome-encapsulated photolyase

Source: Wolf, et al., 2000; Puviani, et al., 2013; Krutmann, et al., 2004.

The mechanisms of DNA repair are essential in maintaining genomic stability in cells. A number of different pathways in place are capable of dealing with different types of DNA damage. Defects in these pathways result in a greater risk of genomic instability and therefore a predisposition to cancer. Impaired DNA repair mechanisms in cancer cells provide an opportunity to exploit this weakness for therapeutic purposes due to their sensitivity to DNA-damaging agents. However, cancer cells often get around this vulnerability by using other repair pathways to deal with damage or by overexpressing DNA repair proteins [39].

Photolyase in Sunscreens. With advancements in skin biology, a number of treatments are now available aiming at the prevention of early aging and skin rejuvenation (Table 2). The main features of an ideal sunscreen are i) capability to scavenge ROS, ii) shielding against UV-A & UV-B radiations, and iii) incorporation of enzymes with DNA repair capability [5]. In a double-blind study by Emanuele et al, it was concluded that sunscreen which contains photolyase and antioxidants (carnosine, atrazine, or ergotheonine) produces a synergistic effect and reduces skin aging [40—42].

The use of DNA repair enzymes encapsulated in liposomes to alleviate UV damage to the skin has been studied for over four decades, involving hundreds of patients and volunteers. As shown in mouse and human studies, in cultured cells, the mechanism by which the enzymes penetrate the skin, access damaged DNA, and stimulate its repair has been outlined, but several details remain unknown. The study suggests that enhancing DNA repair can minimize signs of photoaging and prevent skin cancer. This finding is insufficient; longer-term research is required to determine the significance of DNA damage in skin aging and to confirm its important involvement in the onset and progression of skin cancer [43].

Conclusions. DNA is routinely exposed to all kinds of endogenous and exogenous agents resulting in DNA damage and associated effects. DNA repairing pathways employ numerous enzymes, proteins, and factors in response to DNA damage. DNA damage is the major contributor to the development and progression of cancer and photoaging. All living organisms have enzyme systems for DNA repair. The enzymes are used in a number of skincare products like sunscreens and also in cancer prevention.

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ФЕРМЕНТИ ДЛЯ ВІДНОВЛЕННЯ ДНК ЯК ЛІКУВАЛЬНІ ЗАСОБИ

Пошкодження ДНК — це давно визнаний фактор розвитку та прогресування раку у людини. Нестабільність геному є провідним чинником розвитку раку. У всіх істот є певні шляхи відновлення ДНК та контрольні пункти пошкодження ДНК, без яких функціональна стабільність порушується. Порушення репарації ДНК веде до геномної нестабільності, що призводить до розвитку раку, обмеженого терміну життя та раннього старіння. УФ-промені та іонізуюче випромінювання є основними екзогенними факторами, що відповідають за пошкодження ДНК та викликають її ураження. Ці ураження є причиною фотостаріння. Захист за допомогою звичайного сонцезахисного крему є лише профілактичним. Він не діє, якщо пошкодження вже відбулося. Попит на таку продукцію, яка може скасувати або затримати фотостаріння, зростає, і, таким чином, захист, що забезпечується звичайними сонцезахисними кремами, може бути покращений. Цей огляд зосереджений на останніх розробках щодо участі різних ферментів, що відновлюють ДНК, у лікуванні раку, а також на засобах по догляду за шкірою, таких як сонцезахисний крем.

Ключові слова: *пошкодження ДНК, нестабільність геному, шляхи відновлення ДНК, рак, фотостаріння, сонцезахисний крем.*