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UV Radiation and DNA Repair: The Interplay between Damage Recognition, Repair, and Cancer Risk

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Abstract

Ultraviolet (UV) radiation is a potent environmental mutagen that causes DNA damage, significantly contributing to skin cancer development. The most common forms of UV-induced DNA damage are pyrimidine dimers, particularly thymine-thymine dimers, which distort the DNA structure and impede cellular processes like replication and transcription. To mitigate the consequences of UV-induced lesions, cells have evolved sophisticated repair mechanisms, primarily nucleotide excision repair (NER), which removes bulky DNA adducts, and base excision repair (BER), which handles oxidative DNA damage. The timely recognition and efficient repair of these lesions are crucial to maintaining genomic stability and preventing mutations that could lead to carcinogenesis. This review explores the interplay between UV-induced DNA damage recognition, the activation of repair pathways, and the impact on cancer risk. It discusses the key proteins and enzymes involved in detecting UV-induced lesions, the role of NER in resolving pyrimidine dimers, and the secondary involvement of BER and direct reversal mechanisms. We also examine how defective DNA repair systems, particularly those associated with genetic disorders like xeroderma pigmentosum, heighten the risk of skin cancers. Furthermore, we explore how aging, excessive UV exposure, and genetic mutations influence the efficiency of repair processes and contribute to an increased cancer risk. Understanding these intricate mechanisms is essential for developing preventive strategies and therapeutic interventions aimed at enhancing DNA repair capacity and reducing UV-related cancer incidence. This review emphasizes the importance of targeted therapies and public health measures that could enhance DNA repair and minimize the mutagenic effects of UV radiation.

Keywords: UV radiation; DNA damage; pyrimidine dimers; nucleotide excision repair (NER); base excision repair (BER); direct reversal mechanisms

Introduction

Ultraviolet (UV) radiation, a component of sunlight, is a major environmental factor contributing to DNA damage in skin cells. UV radiation is classified into three types based on wavelength: UV-A, UV-B, and UV-C. While UV-C is largely absorbed by the Earth's ozone layer and does not reach the surface, UV-A and UV-B radiation penetrate the skin and induce a variety of DNA lesions [1]. Among the most common forms of DNA damage caused by UV-B radiation are pyrimidine dimers, particularly thymine-thymine dimers, which form when adjacent pyrimidine bases covalently bond, disrupting the DNA helix and hindering essential processes such as replication and transcription. UV-A radiation, although less energetic, contributes to DNA damage through the generation of reactive oxygen species (ROS), which can cause oxidative lesions that further compromise genomic integrity. If left unrepaired, UV-induced DNA damage can lead to mutations, genomic instability, and the activation of oncogenic pathways that may result in skin cancers, including melanoma, basal cell carcinoma, and squamous cell carcinoma. To protect against such damage, cells have evolved intricate DNA repair mechanisms that recognize, excise, and correct UV-induced lesions, primarily through nucleotide excision repair (NER), base excision repair (BER), and, in some organisms, direct reversal processes. These repair pathways play a critical role in maintaining cellular integrity and preventing the accumulation of mutations that could lead to cancer [2].

Despite these protective mechanisms, the ability of cells to repair UV-induced DNA damage is not always perfect. The efficiency of DNA repair is influenced by factors such as genetic predisposition, aging, and environmental exposures, with impaired repair capacity being a key contributor to the increased susceptibility to skin cancers. Defective DNA repair systems, such as those observed in genetic disorders like xeroderma pigmentosum, underscore the importance of repair mechanisms in preventing UV-induced carcinogenesis. This review aims to explore the complex interplay between UV-induced DNA damage recognition, repair mechanisms, and the impact of impaired repair on cancer risk. By understanding these processes, we can better appreciate the role of DNA repair in preventing skin cancer and the potential therapeutic strategies that could be employed to enhance DNA repair capacity and reduce UV-related carcinogenesis [3].

Discussion

Ultraviolet (UV) radiation is a major environmental carcinogen, with significant implications for skin cancer development. The effects of UV exposure on DNA are profound, as UV radiation can induce a variety of lesions, including pyrimidine dimers, DNA crosslinks, and oxidative damage. These lesions interfere with DNA structure and function, potentially leading to mutations, genomic instability, and tumorigenesis. However, the cell has evolved a range of DNA repair mechanisms to counteract the damage caused by UV radiation. Understanding the molecular processes behind these repairs, as well as their interplay with cancer risk, is critical for devising better prevention and therapeutic strategies [4].

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UV-Induced DNA Damage and Its Recognition

When UV-B radiation interacts with DNA, it primarily induces the formation of pyrimidine dimers, which are covalent bonds between adjacent pyrimidine bases, usually thymine-thymine dimers. These dimers distort the DNA helix, hindering essential processes such as DNA replication and transcription. UV-A radiation, which accounts for the majority of UV exposure, induces damage indirectly by generating reactive oxygen species (ROS) that lead to oxidative base modifications such as 8-oxoguanine. These oxidative lesions can cause mutagenic base-pair substitutions and contribute to the aging process. UV-induced DNA damage is recognized by specialized proteins that initiate repair pathways to maintain genomic integrity. One of the key players in this process is the XPC protein, which is involved in damage recognition in the nucleotide excision repair (NER) pathway. Other proteins, such as XPA and ERCC2, help stabilize the damaged DNA and recruit additional repair factors. In transcription-coupled repair (TCR), damage that obstructs active transcription is preferentially repaired by the action of CSA and CSB proteins, ensuring that the expression of essential genes is not impaired [5].

DNA Repair Mechanisms

The DNA repair process for UV-induced damage is primarily mediated by NER, which is the most efficient pathway for repairing bulky UV-induced lesions. NER functions by recognizing distortions in the DNA structure and excising the damaged region, followed by DNA synthesis to fill the gap. The NER pathway operates in two modes: global genome repair (GGR), which scans the entire genome for damage, and transcription-coupled repair (TCR), which prioritizes repair in the transcribed regions of active genes. The latter mechanism is particularly important in protecting the integrity of critical genes involved in cell cycle regulation and tumor suppression. While NER is the primary repair pathway for UV-induced lesions, base excision repair (BER) also contributes, particularly in the repair of oxidative DNA damage caused by UV-A exposure. In BER, a DNA glycosylase recognizes damaged bases, excises them, and replaces them with the correct nucleotide through a multi-step process that involves cleavage of the DNA backbone and resynthesis. However, BER is less efficient in addressing the bulky pyrimidine dimers that result from UV-B exposure. Direct reversal of DNA damage, though less prominent in UV-induced lesions, also plays a role in repairing some types of oxidative damage. For example, methyltransferases can reverse the methylation of guanine bases, a type of oxidative damage. Photoreactivation, a direct reversal mechanism found in some organisms but not humans, utilizes photolyase enzymes to directly repair thymine dimers by using light energy. Although humans lack functional photolyase, other repair enzymes may help reverse certain UV-induced lesions indirectly [6].

Impaired DNA Repair and Cancer Risk

Despite the effectiveness of DNA repair mechanisms, several factors can impair their function, increasing the risk of UV-induced carcinogenesis. One of the most significant factors is genetic mutations that affect repair proteins. Xeroderma pigmentosum (XP) is a genetic disorder caused by mutations in genes involved in NER, such as XPA, XPC, or ERCC2. Individuals with XP have a dramatically increased risk of developing UV-induced skin cancers due to the inability to repair thymine dimers and other UV-induced lesions efficiently. Similarly, mutations in other repair genes, including those associated with the BRCA pathway, can further elevate the risk of skin cancers and other malignancies [7].

Another factor that contributes to impaired DNA repair and increased cancer risk is aging. As individuals age, the efficiency of DNA repair mechanisms, particularly NER, tends to decline. This decline in repair capacity, combined with the accumulation of DNA damage over time, leads to an increased risk of mutation and cancer development. Age-related changes in the expression and function of repair proteins, along with the accumulation of oxidative damage, can compromise the repair of UV-induced lesions and make cells more vulnerable to carcinogenesis. Environmental factors, particularly chronic and excessive UV exposure, also play a key role in impairing DNA repair capacity. Prolonged UV exposure can overwhelm the repair mechanisms, leading to an accumulation of DNA lesions. In addition, UV-induced DNA damage can induce mutations in genes that regulate repair pathways, further compromising the cell's ability to respond to subsequent DNA damage [8].

Enhancing DNA Repair and Reducing Cancer Risk

Given the critical role that DNA repair plays in preventing cancer, several strategies have been proposed to enhance repair efficiency and reduce the risk of UV-induced skin cancers. One approach involves gene therapy to restore or enhance the function of repair proteins. For example, gene editing techniques like CRISPR could be used to correct defective repair genes in patients with conditions like xeroderma pigmentosum. Another potential strategy is the use of pharmacological agents to stimulate DNA repair pathways [9]. Researchers are exploring small molecules and natural compounds that could enhance NER or BER, improving the efficiency of DNA repair in UV-exposed cells. Some compounds, such as resveratrol and certain antioxidants, have shown promise in promoting DNA repair and reducing oxidative damage, though their effectiveness in clinical settings remains under investigation. Prevention through lifestyle changes, such as avoiding excessive sun exposure and using sunscreens that block both UV-A and UV-B radiation, remains the most effective strategy for reducing the risk of UV-induced DNA damage and skin cancer. Additionally, public health campaigns promoting UV awareness and protective measures can help reduce the overall burden of UV-related skin cancers [10].

Conclusion

UV radiation-induced DNA damage plays a significant role in the development of skin cancers, and the ability to repair this damage is crucial for maintaining genomic stability. Nucleotide excision repair (NER) is the primary pathway for addressing UV-induced lesions, but base excision repair (BER) and direct reversal mechanisms also contribute. Impaired DNA repair, due to genetic defects, aging, or environmental factors, increases the risk of skin cancer. Enhancing DNA repair through gene therapy, pharmacological agents, and antioxidants presents promising avenues for cancer prevention. Ultimately, understanding the molecular processes that govern DNA repair in response to UV radiation will be instrumental in developing strategies to mitigate UV-induced carcinogenesis and improve public health outcomes.

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