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EDITORIAL

Vitamin D3 and inducible DNA repair

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Our body possesses two major protective systems: the immune system and the DNA repair system. The immune system protects us against harmful microorganisms and viruses that invade the body, while the DNA repair system is responsible for safeguarding our genetic material. It protects cellular DNA from genotoxic influences originating internally (for example, reactive oxygen species generated by activated immune cells or cellular metabolism) as well as from a wide range of external physical and chemical exposures (environmental pollutants, diet, tobacco, alcohol, ionizing radiation, and sunlight). Furthermore, DNA is inherently unstable, and spontaneous lesions therefore require continuous correction. It is estimated that tens of thousands of DNA lesions occur daily in every cell of the human body. The most common forms include the loss of DNA bases, oxidative DNA damage, and damage resulting from base alkylation.[1]

DNA damage has a wide range of adverse effects. At the cellular level, it inhibits transcription and replication; causes gene mutations and chromosomal aberrations; activates enzymes and signaling cascades that trigger apoptosis, necroptosis, and other forms of regulated cell death; and induces cellular senescence and metabolic changes. Mutations in genes regulating cell-cycle progression can ultimately lead to malignant transformation and cancer progression. DNA damage also exacerbates many conditions not directly related to cancer, including atherosclerosis and neurodegeneration, by intensifying cellular senescence and inflammatory responses. In brief, DNA repair is essential for our health.

There is a wide variety of DNA lesions, and the processes that eliminate them are equally complex. At least 150 genes, or the proteins and enzymes they encode, are directly involved in DNA repair. In addition, approximately 200 regulatory and accessory factors contribute to genome maintenance, including cell-cycle checkpoint proteins, chromatin modulators, and ubiquitin ligases. Thus, a substantial fraction of the human genome is dedicated to protecting and stabilizing the genome.[2]

DNA repair entails removing damage from DNA and restoring its original state. Another process is known as DNA damage tolerance. In this case, the lesion initially remains in the DNA and is bypassed rather than removed. This mechanism is particularly relevant to bulky adducts that block replication, an event that can otherwise be lethal to the cell. Damage tolerance is a complex process. Nearly a dozen specialized translesion DNA polymerases can bypass particular types of DNA damage and thereby enable replication to proceed in proliferating cells despite the persisting lesion. This may allow the lesion to be carried into the next cell generation, which frequently occurs at the cost of mutations because translesion synthesis is not always error-free. Indeed, many mutations caused by bulky, replication-blocking DNA adducts, including those induced by ultraviolet light, arise during translesion synthesis.

DNA repair and translesion synthesis are clearly cancer-protective mechanisms. Early evidence came from hereditary disorders based on mutations in DNA repair or

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damage tolerance genes, many of which are associated with an extremely high cancer incidence and reduced life expectancy. Numerous such disorders are now known. Several have been described as chromosomal breakage syndromes because patients' cells exhibit high rates of chromosomal aberrations, indicating genomic instability.

As early as 1874, the Viennese dermatologists Ferdinand von Hebra and his son-in-law Moritz Kaposi described a very rare clinical condition in which affected children were extremely sensitive to sunlight. These young patients developed severe skin lesions (keratoses), premature skin aging, and skin tumors at an early age; the condition was named xeroderma pigmentosum (XP). Patients frequently developed not only skin cancer but also other types of tumors. Although some had a short life expectancy, others were less severely affected and lived considerably longer, occasionally for several decades.

Once fibroblast cultures could be established from patients' skin, pioneering studies by James Cleaver and others revealed a repair defect in XP cells.[3] These cells are unable, or only poorly able, to excise UV-induced lesions from their DNA, making them hypersensitive to sunlight. Since then, research has gone far beyond that initial finding by identifying the specific types of DNA damage and elucidating the molecular mechanisms involved in their repair.

It is important to note that this experimental laboratory work used not visible light but high-energy, short-wavelength UV-C, commonly at 254 nm, close to the wavelength at which DNA shows maximal absorption. Irradiation under these conditions produces two critical forms of DNA damage: cyclobutane pyrimidine dimers (CPDs) and pyrimidine(6-4)pyrimidone photoproducts [(6-4)PPs]. The latter are generally repaired rapidly, whereas CPDs are removed more slowly.

In both instances, adjacent pyrimidine bases become covalently linked. These lesions can prevent DNA and RNA polymerases from functioning; consequently, replication and transcription are blocked. In XP cells, the lesions are not removed, or are removed only slowly, compared with normal cells. It took several decades to elucidate the complex nucleotide excision repair mechanism. Approximately 25 proteins recognize the damage, reorganize chromatin to make the lesion accessible, incise the damaged strand on either side of the lesion, remove the resulting oligonucleotide, fill the gap, and seal the DNA.[2] Given the large number of factors involved, it is not surprising that XP comprises several complementation groups caused by mutations in different repair genes. The XP variant (XP-V) is an important exception: nucleotide excision repair is intact, but translesion synthesis across UV-induced CPDs is defective because DNA polymerase eta is absent or inactive. Other, more error-prone polymerases then bypass the lesions, causing high mutation rates and an increased risk of skin cancer.

Given that DNA repair is essential for our health, the question arises as to how much repair activity varies among individuals and whether it can be reinforced. DNA repair capacity does indeed vary among healthy individuals.[4] Unfortunately, comprehensive and reliable data covering all repair enzymes and pathways are lacking. An "atlas" of DNA repair capacity across human organs, combined with interindividual comparisons, would therefore be highly valuable and might eventually help people with low repair capacity to adjust their lifestyles accordingly.

In this context, an important question arises: Is DNA repair upregulated when harmful agents damage the genome? Does the body mount an adaptive response? The findings are sobering: only a small number of repair genes in human cells are transcriptionally upregulated following genotoxic exposure. In total, approximately 25 genes have been reported to be inducible.[5] Four of these—XPF, XPG, DDB2, and XPC—participate in the nucleotide excision repair pathway that is defective in XP. They perform key functions in damage recognition and incision. Their expression can increase following UV irradiation or other genotoxic insults, raising repair protein levels when needed.[6] By contrast, many other repair genes are constitutively expressed at relatively constant levels.

Why is this the case? DDB2 and XPC play crucial roles in recognizing DNA damage and bind avidly to damaged chromatin. An inappropriate excess of these proteins in the nucleus could interfere with DNA metabolism. The situation may be even more critical for XPF-ERCC1 and XPG. These structure-specific endonucleases act like molecular scissors, incising the damaged DNA strand on either side of the lesion so that the damaged segment can be removed. Their activity must be restricted to the correct substrate and coordinated with the subsequent repair steps; otherwise, incision could itself generate harmful strand breaks. This example illustrates that DNA repair must be tightly regulated and coordinated and that an overabundance of repair enzymes is not necessarily beneficial. The appropriate level depends on the extent and type of DNA damage.

This leads to the example of sunlight, to which we are all exposed—to varying degrees and whether intentionally or not. First, a brief note on the experimental studies mentioned above in the context of XP. For decades, such experiments were conducted using short-wavelength UV-C light, commonly at 254 nm, because calibrated UV-C sources are convenient to use in the laboratory.

UV-C produces a characteristic spectrum of DNA lesions, including CPDs and (6-4)PPs, which are highly mutagenic and carcinogenic. We are not normally exposed to solar UV-C because it is absorbed by the atmosphere. We are, however, exposed to longer-wavelength UV-B radiation (280–315 nm). UV-B is required for the cutaneous production of the precursor of vitamin D3, the "sunshine hormone," but it also damages DNA. Some of the lesions are identical to those caused by UV-C, although their relative yields differ. UV-B exposure can additionally generate oxidative DNA damage, which is predominantly processed by base excision repair. These lesions must be removed to limit acute tissue injury and mutations that may eventually promote skin cancer.

The fact that cutaneous vitamin D3 synthesis requires UV-B creates a paradox: an endogenous beneficial hormone is produced in response to a harmful exposure that is genotoxic. It is therefore plausible that vitamin D signaling forms part of a coordinated protective response. This biological relationship, however, does not make intentional sun exposure harmless or establish it as preferable to dietary supplementation.

How is protection mediated? Provitamin D3 is the precursor of a steroid hormone that regulates gene expression. In the skin, UV-B converts 7-dehydrocholesterol to provitamin D3, which then undergoes thermal isomerization to cholecalciferol (vitamin D3)—the same compound commonly taken as a supplement. Cholecalciferol is transported to the liver and converted to 25-hydroxyvitamin D3 [25(OH)D3], the storage form designated as calcidiol. Its circulating concentration is routinely measured to assess vitamin D status, although the optimal target range remains debated. 25(OH)D3 has relatively low biological activity and requires a further conversion step in cells expressing 1alpha-hydroxylase (CYP27B1). These cells produce 1,25-dihydroxyvitamin D3 [1,25(OH)2D3; calcitriol]. Calcitriol binds to the vitamin D receptor (VDR), which heterodimerizes with the retinoid X receptor and binds to regulatory elements in DNA. In a cell-type–dependent manner, vitamin D signaling thus regulates hundreds of genes.

It is particularly interesting that vitamin D signaling influences genes involved in cell-cycle control and the DNA damage response. For example, calcitriol can upregulate p21, a potent cell-cycle inhibitor, and has also been linked to upregulation of GADD45, which has a function in DNA repair. Vitamin D/VDR signaling has also been associated with the regulation of DNA repair factors, including BRCA1, and with enhanced repair of UV-induced lesions in keratinocytes and epidermis.[7,8] XPC and DDB2 are induced by DNA damage triggered by different genotoxicants,[6] whereas XPF and XPG were shown to be upregulated following UV exposure.[9] Whether POLH is also regulated by vitamin D3 remains unresolved. Taken together, the available evidence supports the view that vitamin D/VDR signaling can contribute to the cellular response to UV-induced DNA damage. It does not, however, imply that sunbathing is a safe means of enhancing DNA repair: UV-B creates the genotoxic lesions that the repair machinery must remove, and excessive exposure can overwhelm these defenses.

In summary, nature has linked the cutaneous production of vitamin D3 to protective signaling pathways that may mitigate some of the harmful effects of UV-B radiation. As is generally the case in toxicology, the dose makes the poison: this protective system should not be overburdened.

Conflict of interest

Prof. Dr. Bernd Kaina serves as one of the Editor-in-Chief of this journal. The author declares no conflict of interest.

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