Stopping DNA Damage: A Newly Discovered Protein-Enhancing DNA Repair Mechanisms

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ABSTRACT

Endogenous factors, such as reactive oxygen species, and exogenous factors, including ionizing radiation, ultraviolet light, and chemical agents frequently cause DNA damage. This damage compromises genomic stability, leading to mutations, cellular dysfunction, and diseases such as cancer and neurodegenerative disorders. To counteract these threats, cells utilize DNA repair pathways including direct reversal, base excision repair, nucleotide excision repair, mismatch repair, and double-strand break (DSB) repair. These mechanisms are essential for maintaining genomic integrity and ensuring the accurate transfer of genetic information.

Deinococcus radiodurans exhibits extraordinary resistance to DNA-damaging agents through a combination of strategies, including an efficient DNA repair system and specialized DNA damage response proteins. Among these, DdrC is a unique DNA-binding protein that recognizes and stabilizes damaged DNA, preventing single-strand breaks from escalating into DSBs. Structural studies show that DdrC functions as a dimer with two distinct DNA-binding sites, enabling it to scan DNA for lesions and compact damaged regions. This compaction not only stabilizes DNA but also aids in preserving nucleoid integrity under extreme conditions.

The ability of DdrC to bind and compact damaged DNA suggests potential applications in medicine and biotechnology. In cancer therapy, DdrC could disrupt repair mechanisms in tumor cells, enhancing the effects of existing treatments. Its role in stabilizing DNA makes it a candidate for mitigating age-related genomic instability and protecting neurons in neurodegenerative diseases. However, challenges remain, including its bacterial origin, the need for adaptation to human systems, and the development of precise delivery methods.

This review provides an overview of DNA damage and repair mechanisms, the properties of DdrC, and its potential for advancing DNA repair-based therapies. While further research is required, DdrC represents a promising step toward innovative approaches to addressing genomic instability.

Keywords: DNA damage, DNA repair mechanisms, DNA repair and aging, DdrC protein, Genomic stability

Introduction

DNA, the fundamental blueprint of life, is constantly subjected to various threats that compromise its integrity and functionality. DNA damage can arise from both endogenous sources, such as reactive oxygen species (ROS), and exogenous factors, including ultraviolet (UV) light, ionizing radiation, and genotoxic chemicals.[1] This damage disrupts essential processes like replication and transcription, posing a significant risk to genomic stability (Figure 1). The consequences of DNA damage extend far beyond cellular dysfunction, playing a central role in human pathobiology. Conditions such as birth defects, cancer, premature aging syndromes, and certain neurologic disorders are all associated with disruptions in DNA repair mechanisms.

The importance of DNA repair in maintaining health was first underscored four decades ago when Cleaver identified defective DNA repair as a key factor in the development of cancer and neurological disease in children with xeroderma pigmentosum (XP). XP patients exhibit severe neurologic phenotypes, including ataxia, microcephaly, deafness, learning disabilities, and peripheral neuropathy.

Neuropathological findings in these patients include significant loss of large sensory fibers and dorsal root ganglion cells, along with cerebellar and cerebral atrophy.[2] These observations emphasize the critical role of DNA repair in protecting against a wide array of diseases.

The relationship between DNA damage and aging has also been extensively studied. The DNA damage theory of aging proposes that the accumulation of unrepaired DNA lesions, such as breaks, cross-links, and oxidative modifications, contributes to genomic instability and the aging process. This theory aligns with the broader concept that aging results from a decline in molecular fidelity, particularly after the reproductive period, when natural selection is thought to exert less pressure to maintain biomolecular integrity.[3] Mouse models of nucleotide excision repair (NER) syndromes strongly support this theory, showing a clear link between the extent of DNA repair deficiencies and the severity of accelerated aging phenotypes.[4,5] Furthermore, human studies have revealed that single-nucleotide polymorphisms in DNA repair genes that enhance repair capacity are associated with increased longevity, underscoring the critical role of these pathways in determining lifespan.[6]

The complexity and importance of DNA repair are reflected in the human genome, where more than 125 genes encode proteins directly involved in these processes.[7] Deficient repair mechanisms allow the accumulation of DNA damage, leading to genomic instability and disease, while enhanced repair pathways are associated with improved healthspan and longevity. These insights highlight the central role of DNA repair in preserving genomic stability and preventing the progression of various diseases, including cancer, neurodegeneration, and premature aging.

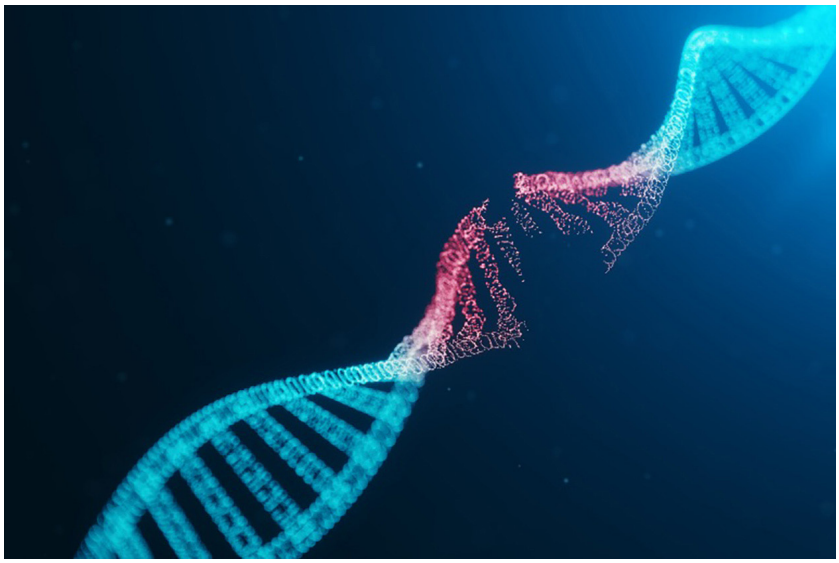

Fig 1 | DNA damage can occur from both endogenous and exogenous factors. This damage impairs critical processes such as replication and transcription potentially causing lethal disorders

Mechanisms of DNA Damage

Endogenous sources of DNA damage generally come from normal cellular metabolic processes. ROS, generated during oxidative stress, are a major factor, inducing base lesions, sugar damage, and even strand breaks. For instance, radiolysis of water by ROS can lead to base modifications,[8] while free radical insults can cause sugar damage such as 8,5'-cyclopurine-2'-deoxynucleosides.[9,10] Additionally, spontaneous chemical reactions like depurination, depyrimidination, and cytosine deamination frequently occur, altering the DNA sequence and structure.

Exogenous factors include environmental hazards such as UV light, ionizing radiation, toxic heavy metals, and genotoxic chemicals.[11] These agents directly interact with DNA, causing a variety of structural damages, including single-strand breaks, double-strand breaks (DSBs), and cross-linking.[12] For example, chemical cross-linking agents like cisplatin can hinder critical enzymatic activities of DNA helicases and polymerases, further exacerbating the damage.[13]

The spectrum of DNA damage includes single-strand breaks, DSBs, base damage, sugar damage, DNA cross-linking, and clustered damage sites. Among these, DSBs represent the most severe threat to cellular viability.[14] Without effective repair or if repaired erroneously, DSBs can lead to carcinogenesis or trigger cell death. Similarly, DNA cross-links, caused by environmental or chemotherapeutic agents, trap repair proteins and impede DNA replication and transcription.

DNA damage poses a profound challenge to genomic stability, a critical requirement for survival and reproduction. Genomic instability is closely linked to various pathological conditions, including cancer, aging, birth defects, and neurological disorders. For instance, continuous activation of proto-oncogenes or suppression of tumor suppressor genes due to persistent DNA damage can initiate and propagate cancer development.[15] Furthermore, errors introduced during replication or repair can disrupt cellular processes, leading to apoptosis or uncontrolled cell proliferation.

DNA damage occurs via direct or indirect mechanisms. In direct damage, exogenous or endogenous agents physically break chemical bonds within the DNA molecule, altering its structure and activity. Indirectly, metabolic byproducts or secondary effects from cell damage, such as loss of membrane integrity, generate toxic intermediates that interact with DNA, causing further degradation.

DNA Repairing Mechanisms

DNA repair is an essential cellular process required to counteract the constant threats posed by endogenous and exogenous sources of DNA damage. Unlike other biomolecules, DNA cannot be replaced once damaged and must instead be repaired to preserve the integrity of genetic information and ensure proper cellular function. Failure to effectively repair DNA damage can lead to genomic instability, which increases the risk of mutations, cancer development, and various hereditary disorders. The importance of DNA repair mechanisms is highlighted by the severe consequences of their dysfunction, including genomic defects, malignant transformation, and the progression of cancer. Moreover, disrupted repair processes often enable cancer cells to survive, undermining the efficacy of chemotherapeutic and radiotherapeutic interventions.

In recent years, extensive research has demonstrated the critical role of DNA repair pathways in cellular homeostasis. Certain repair components are so vital that life cannot be sustained without them. For example, the ATR protein, essential for early embryonic development, is necessary to prevent chromosomal fragmentation, with its deficiency leading to embryonic lethality.[16] Similarly, hereditary disorders such as XP, characterized by an inability to repair UV-induced DNA damage, underscore the clinical significance of effective repair mechanisms in human health.[17]

Multiple DNA repair pathways exist to address the diverse types of damage that DNA can sustain (Figure 2). Direct reversal repair is the simplest and most economical mechanism, involving the correction of specific lesions without excision or replacement of DNA segments. This mechanism includes the repair of O-alkylated DNA damage by alkyltransferases and dioxygenases, as well as the reversal of UV-induced photolesions by photolyases.[18,19] Base excision repair (BER) is another critical pathway that addresses small base lesions caused by oxidative stress or alkylation. Key enzymes such as OGG1 recognize damaged bases, initiating a repair process that replaces one to ten nucleotides through short- or long-patch repair, thereby preserving DNA integrity with minimal structural disruption.[20,21]

NER, by contrast, is a more complex process designed to address bulky adducts and cross-linking damage that significantly distort the DNA helix.[22]

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This pathway operates through two sub-processes: (1) *transcription-coupled repair*, which prioritizes lesions in active transcription regions, and (2) *global genome repair*, which scans the entire genome for damage. Deficiency in NER is strongly associated with several human diseases, including XP and neurological disorders, reflecting the pathway's critical role in maintaining genomic stability.[23]

Mismatch repair (MMR) is another vital repair mechanism that safeguards replication fidelity by correcting single nucleotide mismatches and small insertion-deletion loops introduced by DNA polymerase during replication. The process involves the recognition of mismatches by protein complexes such as MSH2-MSH6, which form a sliding clamp around the DNA lesion to initiate repair.[24] By counteracting replication errors, MMR significantly enhances genomic accuracy.

Among the various forms of DNA damage, DSBs represent the most severe threat to genomic stability. These breaks are repaired through homologous recombination or non-homologous end joining, mechanisms that restore the integrity of the DNA double helix.[25] The accurate repair of DSBs is essential for preventing mutations that could otherwise lead to carcinogenesis or cell death.

While some repair mechanisms, such as BER and direct reversal repair, are relatively straightforward, others, like NER and DSB repair, involve intricate and multistep processes. The complexity of these pathways reflects the diverse and often severe nature of DNA damage. Deficiencies in any of these mechanisms are closely linked to the development of diseases, particularly cancer, where unresolved DNA damage contributes to mutation accumulation and tumor progression.

DdrC, a Unique DNA Repair Factor

Deinococcus radiodurans, a gram-positive bacterium, is renowned for its extraordinary resistance to DNA-damaging conditions, including ionizing radiation, UV light, desiccation, and oxidative stress.[26] This resilience arises from a combination of mechanisms that preserve proteome and genome integrity: a high intracellular Mn/Fe ratio that minimizes oxidative damage, highly efficient DNA repair systems, and a compact nucleoid structure that limits DNA fragment dispersion, facilitating repair.[27] During the radiation-desiccation response, ddrC is one of the most upregulated genes, alongside other DNA damage response genes such as ddrA, ddrB, ddrD, and pprA.[28] These proteins, specific to *Deinococcus* species, are rapidly recruited to the nucleoid following DNA damage, where they perform specialized roles in repair.

DdrC is a 25 kDa DNA-binding protein that demonstrates distinct binding behaviors under varying DNA conformations (Figure 3). In experiments using supercoiled, relaxed, and linear forms of plasmid DNA, high concentrations of DdrC induce the formation of large intermolecular complexes that remain in the gel wells, while lower concentrations result in smaller complexes that migrate within the gel.[28,29]

Notably, relaxed DNA displays an unexpected increase in plasmid mobility upon DdrC binding. This atypical behavior suggests three possible scenarios: the DNA-protein complex may acquire a more negative

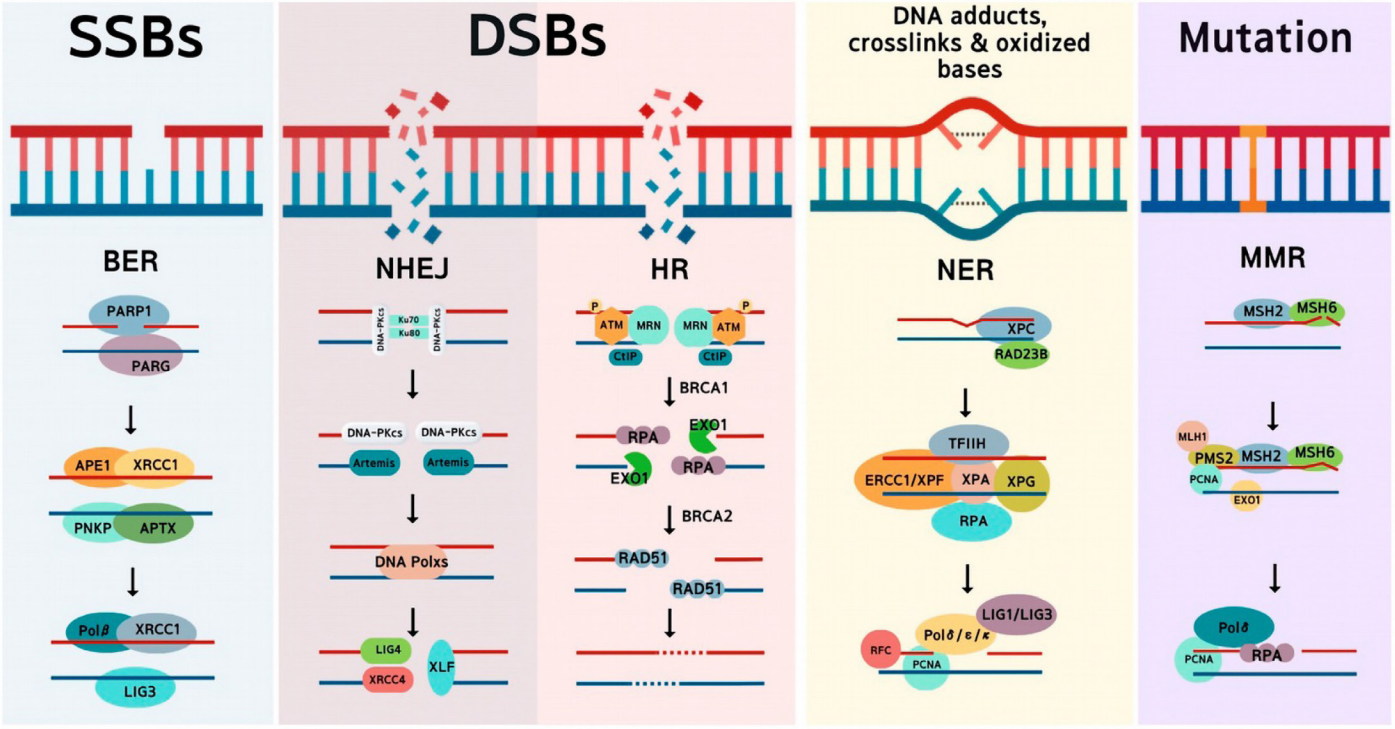

Fig 2 | Types of DNA damage and repair mechanisms

Credit: DNA Damage and Its Role in Cancer Therapeutics, doi.org/10.3390/ijms24054741

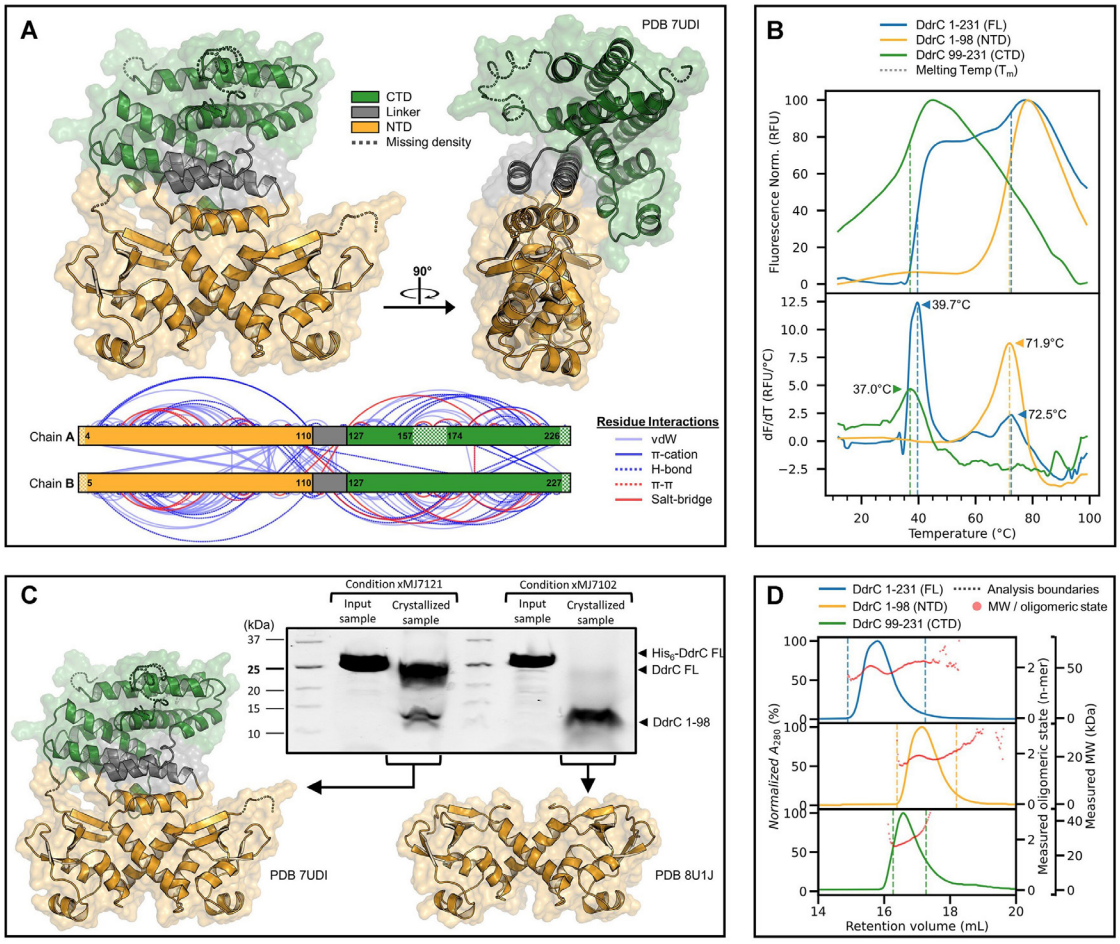

Fig 3 | Structural analysis of DdrC domains. (A) The crystal structure of the full-length DdrC homodimer. (B) Differential scanning fluorimetry profiles for three DdrC variants. (C) The crystal structure of a proteolytically degraded sample of DdrC. (D) SEC-MALS analysis of the oligomeric states of three DdrC variants

Credit: Nucleic Acids Research, doi.org/10.1093/nar/gkae635

charge, undergo nuclease-induced shortening, or experience topological changes reducing its radius of gyration.[30]

DdrC binds to both single- and double-strand DNA breaks. Structural and functional studies reveal that the DdrC dimer contains two asymmetrical DNA-binding sites, supported by distinct positive electrostatic surface potentials. Computational modeling indicates that one binding site adopts an open conformation to transiently bind DNA, while the second remains closed until a lesion is detected.[30] This asymmetry enables DdrC to scan DNA for damage and respond to ss- or ds-breaks through conformational changes. Interactions with ss- or ds-breaks involve residues in the N-terminal domain (NTD), while the carboxy-terminal domain (CTD) facilitates core DNA binding.

When DdrC detects a break in DNA, it undergoes a conformational change that opens the second binding site, allowing the dimer to trap additional DNA lesions (Figure 4). This mechanism is proposed to involve stored tension forces within the dimer, particularly in the deformed α6 helix connecting the NTD and CTD. The straightening of this helix likely drives the conformational change, supported by ionic interactions between the NTD of one chain and the CTD of the other. This clasping mechanism stabilizes the asymmetric state, counteracting the tension until triggered by DNA damage. Once activated, DdrC traps ss-breaks, preventing their progression to ds-breaks and compacting the DNA.[30]

DdrC's ability to compact and circularize damaged DNA is critical for the survival of *D. radiodurans* under extreme conditions. This compaction minimizes the risk of further damage, such as diffusion of DNA ends or escalation of ss-breaks to ds-breaks. Experimental evidence using precisely nicked and linearized plasmids supports this role, showing that DNA compaction increases proportionally with the degree of damage. In vivo, DdrC co-localizes with compact nucleoid structures in response to γ-radiation, reinforcing its function as a nucleoid-associated protein.[30]

Crystal structures of DdrC reveal the molecular basis of its dual-DNA-binding sites. While both sites involve residues from opposing chains of the dimer, their structural configurations differ. Functional assays demonstrate that mutations disrupting either DNA binding or lesion recognition significantly impair UV-C resistance, confirming that both functions are essential for DdrC's

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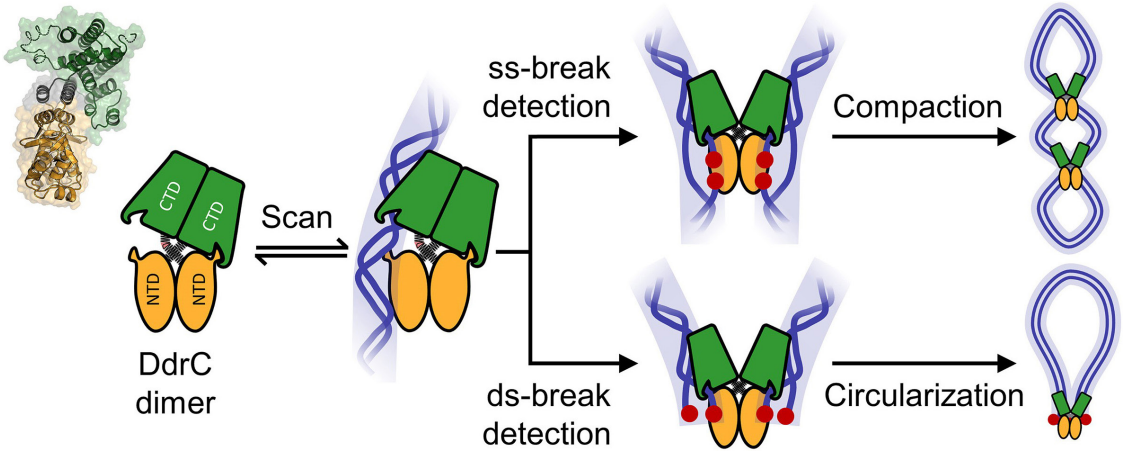

Fig 4 | DdrC repairing broken DNA

Credit: Nucleic Acids Research, doi.org/10.1093/nar/gkae635

activity.[30] The CTD primarily mediates DNA binding, while the NTD interacts with lesions, triggering conformational changes that facilitate further repair.

The compaction behavior of DdrC parallels mechanisms observed in other DNA repair systems, such as PARP-1 in human cells and Rad4/XPC in inter-base adduct recognition.[30] However, unlike these systems, which target single lesions, DdrC uniquely traps two DNA breaks per dimer, enabling it to stabilize complex damage and control genome topology.

The role of DdrC extends beyond lesion binding and repair. Its ability to compact DNA and neutralize ss-breaks positions it as a critical factor in maintaining nucleoid integrity under stress. The dominant-negative effects observed in DdrC mutants deficient in DNA binding or nick recognition suggest additional roles, potentially involving interactions with other nucleoid-associated proteins or recruitment of repair factors. This multifunctionality makes DdrC indispensable for the remarkable DNA damage resistance of *D. radiodurans*.

Potential Applications in Medicine

DdrC, a DNA repair protein from *D. radiodurans*, holds significant potential for therapeutic and biotechnological applications due to its unique ability to bind and stabilize DNA at sites of damage. Its role in recognizing and compacting damaged DNA makes it a promising candidate for addressing conditions where genomic instability is a key factor, such as cancer, neurodegenerative diseases, and aging-related disorders.

In cancer, genomic instability drives tumor progression and resistance to therapies like chemotherapy and radiotherapy. These treatments rely on overwhelming cancer cells with DNA damage, but many tumors adapt by enhancing their repair mechanisms. DdrC's ability to bind DNA breaks and compact damaged regions could interfere with these repair pathways. By targeting DdrC to tumor cells, it might be possible to limit their ability to recover from treatment-induced damage, making them more susceptible to existing therapies.

The accumulation of DNA damage is also a hallmark of aging, contributing to cellular senescence and loss of function in tissues over time. DdrC's ability to stabilize and compact damaged DNA may provide a way to reduce the impact of these lesions. By preventing single-strand breaks from escalating into more severe DSBs, DdrC could help maintain genomic stability in aging cells.

Neurons, with their high metabolic activity and limited capacity for repair, are particularly vulnerable to DNA damage. This makes neurodegenerative diseases like Alzheimer's and Parkinson's possible areas where DdrC-based approaches could have an impact.

Limitations

The use of DdrC in therapeutic applications faces several significant limitations. First, as a bacterial protein, DdrC is not naturally compatible with human cellular systems. Its interactions with human DNA and repair machinery remain unexplored, and it is unclear whether its activity could disrupt tightly regulated repair pathways in human cells. This raises the risk of unintended genomic instability or interference with essential cellular processes.

DdrC's specificity for certain types of DNA lesions, while advantageous, could also be a limitation. Its interactions with non-damaged or minimally damaged DNA are not well understood, and any off-target binding could lead to disruptions in gene expression or replication. Additionally, its DNA compaction activity, while protective in bacterial cells, could potentially hinder essential DNA processes in human cells, such as transcription or replication.

The delivery of DdrC to human tissues is another significant challenge. Effective targeting requires precise delivery systems, such as nanoparticles or engineered viral vectors, but these methods carry risks, including immune reactions, limited tissue specificity, and the possibility of off-target effects.

Furthermore, DdrC's structural stability and function may not translate seamlessly to the human cellular environment, which differs significantly from that

of *D. radiodurans*. Its dimerization and conformational changes, critical for its activity, may be impaired in human cells.

Conclusion

DdrC is a unique DNA repair protein with promising potential for medical and biotechnological applications. Its ability to bind DNA lesions, stabilize damaged sites, and compact DNA offers a novel approach to addressing genomic instability, a key factor in diseases like cancer, neurodegenerative disorders, and aging-related conditions. However, realizing this potential requires overcoming significant challenges.

In cancer treatment, DdrC could disrupt repair mechanisms in tumor cells, increasing their vulnerability to existing therapies like chemotherapy and radiotherapy. In aging and neurodegenerative diseases, it may help preserve genome integrity by preventing the progression of DNA damage. Its ability to stabilize DNA could also make it a valuable tool in genetic engineering and DNA preservation.

Despite its potential, DdrC's bacterial origin raises concerns about its compatibility with human cells. Its long-term effects on healthy DNA and cellular processes remain unknown, and its delivery to specific tissues is a major hurdle. Further research is needed to adapt DdrC for use in human systems, ensure its safety, and develop precise delivery methods.

DdrC highlights the possibility of using nature's sophisticated repair mechanisms to improve human health. Focused investigation and careful adaptation could lead to innovative therapies and tools for managing diseases associated with DNA damage.

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