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Oxidative Stress-Induced DNA Damage and Repair Pathways in Cellular Senescence and Age-Related Pathologies: Mechanistic Insights and Therapeutic Implications

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ABSTRACT
Aging is a multifaceted biological process associated with increased oxidative stress, leading to cumulative DNA damage and genomic instability. Oxidative DNA damage contributes significantly to age-related diseases, including neurodegenerative disorders, cardiovascular diseases, and cancer. This review explores the molecular mechanisms of oxidative stress-induced DNA lesions, their impact on cellular senescence, and the intricate network of DNA repair pathways that counteract this damage. We highlight recent advances in understanding oxidative DNA repair mechanisms, their dysregulation in aging, and potential therapeutic interventions aimed at mitigating oxidative stress and preserving genomic integrity.

1. INTRODUCTION

Oxidative stress arises when the production of reactive oxygen species (ROS) exceeds the capacity of cellular antioxidant defenses, resulting in damage to vital macromolecules such as lipids, proteins, and nucleic acids. Among these, oxidative DNA damage is particularly detrimental, as it can lead to mutations, genomic instability, and impaired cellular function. Accumulation of DNA lesions over time contributes to cellular aging and increases susceptibility to age-related diseases, including neurodegenerative disorders, cardiovascular diseases, and cancer.One of the primary mechanisms by which cells combat oxidative DNA damage is through highly efficient DNA repair pathways, including base excision repair (BER), nucleotide excision repair (NER), and double-strand break repair. These pathways play a crucial role in preserving genomic integrity and delaying the onset of age-associated functional decline. However, aging is often accompanied by a decline in the efficiency of these repair mechanisms, exacerbating DNA damage accumulation and accelerating cellular senescence.This section explores the intricate relationship between oxidative stress and aging, highlighting the critical role of DNA repair in maintaining cellular homeostasis. Understanding these mechanisms may offer potential therapeutic strategies to enhance DNA repair capacity, mitigate

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oxidative damage, and promote healthy aging.

2. Mechanisms of Oxidative Stress-Induced DNA Damage

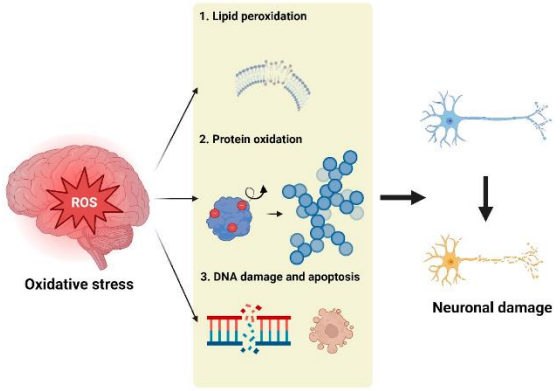

Fig.Oxidative Stress-Induced DNA Damage

ROS, such as superoxide anions, hydrogen peroxide, and hydroxyl radicals, interact with DNA, causing base modifications, strand breaks, and crosslinking. The most common oxidative DNA lesion, 8-oxo-7,8-hydroxyguanine (8-oxoG), leads to mutagenesis and genomic instability. This section elaborates on the biochemical pathways underlying ROS generation and the specific types of oxidative DNA damage encountered in aging cells.

Table 1: Types of Oxidative DNA Damage and Their Consequences

Type of Damage	Mechanism	Consequence
8-oxoG	Guanine oxidation	G → T transversion mutations
AP Sites	Loss of base	Strand instability
DNA Strand Breaks	ROS-induced cleavage	Genomic instability, apoptosis

3. DNA Repair Pathways Counteracting Oxidative Damage

Cells deploy multiple DNA repair pathways to correct oxidative lesions and maintain genome integrity. The key mechanisms include:

- **Base Excision Repair (BER):** The primary pathway for repairing 8-oxoG and other oxidized bases, facilitated by DNA glycosylases such as OGG1 and APE1.
- **Nucleotide Excision Repair (NER):** Addresses bulky oxidative lesions and crosslinks that distort DNA helical structure.
- **Mismatch Repair (MMR):** Plays a role in correcting oxidative base mispairing.
- **Homologous Recombination (HR) and Non-Homologous End Joining (NHEJ):** Repair DNA double-strand breaks induced by oxidative stress.

Recent studies suggest that deficiencies in these pathways accelerate aging phenotypes and increase susceptibility to neurodegeneration and cancer. This section provides structural and functional insights into these repair mechanisms.

4. Oxidative DNA Damage and Cellular Senescence

Accumulation of oxidative DNA damage triggers cellular senescence, a state of irreversible cell cycle arrest that contributes to aging and age-related pathologies. Senescent cells exhibit persistent DNA damage response (DDR) activation, pro-inflammatory secretory phenotypes (SASP), and telomere attrition. This section discusses the interplay between oxidative stress, DDR activation, and the molecular drivers of senescence, emphasizing its role in aging and chronic disease progression.

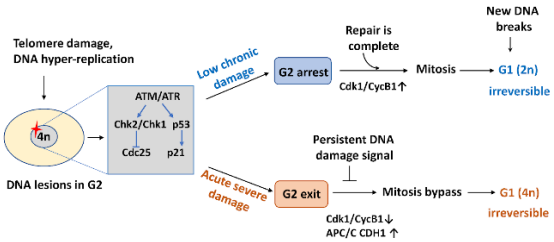

Figure 1: Pathways Linking Oxidative DNA Damage to Cellular Senescence

5. Oxidative DNA Damage in Age-Related Diseases

Oxidative DNA damage is a hallmark of multiple age-related disorders:

- **Neurodegenerative Diseases:** Elevated oxidative damage is observed in Alzheimer's and Parkinson's disease, leading to neuronal loss and cognitive decline.
- **Cardiovascular Diseases:** ROS-induced endothelial DNA damage promotes atherosclerosis and myocardial dysfunction.
- **Cancer:** Genomic instability from defective oxidative DNA repair increases oncogenic mutations and tumorigenesis.

This section integrates recent findings on oxidative DNA damage in disease pathology, offering insights into potential biomarkers and therapeutic targets.

6. Therapeutic Strategies Targeting Oxidative DNA Damage

Several therapeutic approaches aim to mitigate oxidative DNA damage and enhance repair capacity, including:

- **Antioxidant Therapies:** Dietary polyphenols (e.g., resveratrol, curcumin) and pharmacological agents that neutralize ROS.
- **DNA Repair Enhancers:** Small molecules that activate repair enzymes such as PARP1 and OGG1.
- **Senolytics:** Compounds that selectively eliminate senescent cells, reducing chronic

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inflammation and tissue dysfunction.

- **Gene Therapy Approaches:** CRISPR-based interventions targeting defective repair genes.

Table 2: Emerging Therapeutics for Oxidative DNA Damage Mitigation

Therapeutic Approach	Mechanism	Clinical Application
Antioxidants	ROS scavenging	Alzheimer's, cardiovascular diseases
DNA Repair Activators	BER pathway stimulation	Cancer prevention, neuroprotection
Senolytics	Clearance of senescent cells	Aging-related chronic diseases

7. CONCLUSION AND FUTURE DIRECTIONS

Oxidative DNA damage plays a crucial role in aging and age-related diseases by promoting genomic instability, cellular senescence, and disease susceptibility. A deeper understanding of DNA repair mechanisms and their regulation holds promise for developing targeted interventions to mitigate age-associated pathologies. Future research should focus on personalized therapeutic strategies integrating antioxidant therapy, senescence modulation, and DNA repair enhancement.

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