Review Article

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ROLE OF DNA REPAIR IN AGING AND MALIGNANCY

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ABSTRACT

DNA repair enzymes are proteins that detect and repair physical damage to DNA induced by radiation, ultraviolet light, or reactive oxygen species. The repair of DNA damage prevents the loss of genetic information, the creation of double-strand breaks, and the formation of DNA crosslinks. The time-dependent reduction of functional properties is known as aging. Mitochondrial malfunction and the buildup of genetic damage are two common factors of aging. In fact, the poor maintenance of nuclear and mitochondrial DNA is likely a major factor in aging. When the DNA repair machinery isn't operating fine, DNA lesions and mutations can occur, which can lead to cancer development. In fact, the poor maintenance of nuclear and mitochondrial DNA is likely a major factor in aging. When the DNA repair enzymes isn't operating fine, DNA lesions and mutations can occur, which can lead to cancer development. The large number of alterations per cell, which can reach 105, has been identified as a driving mechanism in oncogenesis. These findings show that abnormalities in the DNA repair pathway contribute to the senescence as well as cancer. Nucleotide excision repair (NER), base excision repair (BER), double-strand break repair, mismatch repair (MMR), are all major DNA repair processes in mammalian cells. BER excises mostly oxidative and alkylation DNA damage, NER removes bulky, helix-distorting lesions from DNA (e.g., ultraviolet (UV) photodimers), MMR corrects replication errors.

KEYWORDS: DNA repair, Aging, Malignancy, Single-strand breaks (SSBs), Double strand breaks (DSBs).

INTRODUCTION

Neurodegeneration, cancer, and other chronic disorders are all linked to aging (1). The functional deterioration in multiple organ systems in older adults appears to be caused by no single molecular process. However, one popular idea holds that molecular damage, such as DNA damage and mutations, accumulates over time in mature organisms and has phenotypic repercussions. The functional deterioration in multiple organ systems in older adults appears to be caused by no single molecular process. However, one popular idea holds that molecular damage, such as DNA damage and mutations, accumulates over time in mature organisms and has phenotypic repercussions (2).

DNA is a rare and valuable molecule. It stores crucial information on the content and function of cells. Each chromosome has just two copies in the cell, and if the sequence is gone, there is no way to replace it. The irreplaceability of DNA distinguishes it from other biological molecules, making it a prime target for age-related degradation. Cells have created sophisticated DNA repair mechanisms to prevent DNA damage. Surprisingly, DNA repair can suffer from aging-related alterations and degradation.

Initially, there was little interest in the role of DNA repair in cancer because it was assumed that its main function was to deal with DNA damage removal. It is now well understood that lesions that are not removed collect, causing a cell to undergo malignant transformation. The occurrence of the mutator phenotype has been suggested as a result of an increasing number of molecular abnormalities. (3). According to some estimates, each cancer genome has up to 105 mutations. Because not all somatic mutations make contributions to carcinogenesis, they were separated into two categories: "driver" and "passenger." The term utilized expresses their significance in a straightforward manner. (4). DNA repair gene mutations aren't commonly seen among cancer driver mutations. Deregulation of DNA repair in cancer cells should be viewed as a change in the DNA damage response, which encompasses DNA repair, cell cycle, and apoptosis gene alterations. (5). In any case, altered cells remain under the constant monitoring of DNA repair machinery, preventing the accumulation of damage that would otherwise cause the cell to die (6). As a result, rather than gene mutations, a modified DNA repair potential

should be calculated in relation to genetic polymorphism. The present state of knowledge about the role of DNA repair in aging and cancer is discussed in this article.

Review of literature-

DNA DAMAGE AND DNA REPAIR PATHWAYS AND AGING

Physical and chemical agents are constantly harming nucleic acids, proteins, and lipids. Radiation, nutrition, and environmental pollutants are all external contributors of DNA damage. Chemical instability, such as depurination, spontaneous mistakes during DNA replication and repair, and reactive oxygen species (ROS), which are by-products of normal metabolism, are all endogenous sources of DNA damage. Base alterations, single-strand breaks (SSBs), double-strand breaks (DSBs), and interstrand cross-links are thought to be generated by ROS in as many as 50,000 human cells every day (7). Nucleotide excision repair (NER), base excision repair (BER), double-strand break repair, mismatch repair (MMR), are all major DNA repair processes in mammalian cells. BER excises mostly oxidative and alkylation DNA damage, NER removes bulky, helix-distorting lesions from DNA (e.g., ultraviolet (UV) photodimers), MMR corrects replication errors, while DSBR corrects DSBs, primarily through error-prone reconnecting of broken DNA end points (nonhomologous end joining (NHEJ) or precisely mending the DSB utilizing information from the undamaged sister chromatid (homologous recombination (HR) (8).

Aging is a complex physiological process that causes physiological integrity to deteriorate over time. Aging is a result of the accumulation of cellular damage. Although numerous cellular elements may be damaged as a result of aging, research suggests that DNA is the primary target in this process. (9); As a result, genomic instability is the most common cause of aging (10,11,12). Since unrepaired DNA damage, DNA mutations, and epimutations aggregate in an age-related fashion, genome instability has been identified as a cause of aging. (13).

EVIDENCE FOR AGE-RELATED CHANGES IN DNA REPAIR FROM THE STUDIES OF SOMATIC MUTATIONS

Aging is said to be caused by the buildup of somatic harm, according to popular belief. Aging is said to be caused by the buildup of somatic harm, according to popular belief. The genetic mutations do not harm the cell, but when they accumulate in large enough quantities, they can cause transcriptional dysregulation (14), decreased fitness, and eventually the aging phenotype.

AGE-RELATED CHANGES IN MISMATCH REPAIR (MMR)

MMR corrects mispaired bases caused by replication mistakes, recombination between inadequately matched sequences, and 5-methyl-cytosine deamination. A point mutation would occur if DNA replication continued through a mismatched base pair. The MMR mechanism is also thought to have a role in the repair of oxidative damage through unknown mechanisms. (15). Several lines of evidence point to the MMR system's role in the aging process. MMR is required for the maintenance of repeating sequences, as MMR gene mutations are linked to a significant destabilization of microsatellites (16), and microsatellite instability rises with age in humans. (17,18, 19).

AGE-RELATED CHANGES IN BASE EXCISION REPAIR (BER)

A variety of experimental methodologies have been used to investigate age-related variations in BER. Senescent human fibroblasts and leukocytes from elderly donors have larger basal levels of AP sites than young cells, according to a study that measured the amounts and kinetics of AP sites following DNA damage in nuclear DNA (20). The level of AP sites rose faster in the young cells than in the old cells after treatment with H2O2 or MMS, indicating a lack in DNA glycosylase activity (21).

AGE-RELATED CHANGES IN NUCLEOTIDE EXCISION REPAIR (NER

Short DNA oligonucleotides with a broken base are removed by NER (22). NER detects bulky lesions generated by carcinogenic chemicals, as well as UV-induced covalent connections between neighboring pyrimidines.

AGE-RELATED CHANGES IN DOUBLE-STRAND BREAK (DSB) REPAIR

The most deadly of all DNA lesions is a double strand break (DSB). A DSB causes the loss of chromosomal segments and puts the cell's viability in jeopardy if it is not repaired. Misrepaired DSBs, which destabilize the genome and cause genomic rearrangements, are also harmful to the organism. In aged species, genomic rearrangements are widespread (23,24-28), eventually leading to transcriptional dysregulation (29) and cancers. There is enough evidence that all DNA repair processes, including MMR, excision repair, and DSB repair, become less efficient with age, resulting in mutation accumulation. The origins of this degradation are even less well understood. Several investigations have found that the expression or activity of DNA repair enzymes decreases with aging. (30-

33,34,35,36). Why do DNA repair enzyme levels drop as people become older, and why are all DNA repair mechanisms affected? Because DNA repair and DNA damage response are closely regulated processes, it's tempting to believe that as people age, their DNA damage response becomes less efficient or disregulated. Changes in the response of DNA repair proteins to DNA damage have been described as well (37-39,40,41,42,43). Another mechanism driven by DNA damage, apoptosis, has been demonstrated to be downregulated in aging (44) and senescence , which has been linked to decreased p53 activity. (45). Beyond the DNA damage response, it is widely assumed that as organisms age, they become more susceptible to stress, and hence their stress responses may change. The stress response caused by DNA damage and insulin/IGF1 signaling have recently been linked (46). As stress signaling becomes more erratic as people become older, it may have an impact on DNA repair.

Numerous external and internal genotoxicants continuously expose genomic and mitochondrial DNA molecules to their harmful effects. As a result, organisms developed a protection system called the DNA repair process.

DNA REPAIR DEFECTS LEAD TO TUMOR DEVELOPMENT

Xeroderma pigmentosum (XP), trichothiodystrophy (TTD) and Cockayne syndrome (CS) are rare autosomal recessive disorders caused by mutations in the nucleotide excision repair (NER) system, which protects DNA from UV damage (47). Indeed, dermatologists were the first to describe XP, which was the first condition linked to a malfunction in a DNA processing system.

The NER-associated disorders all include enhanced UV sensitivity and freckling in sun-exposed skin areas, but although XP is a skin cancer-prone disease (48) (>1000-fold increase), CS and TTD are not. Mutations can result from the bypass of unfixed DNA lesions while replication in proliferating cells of XP patients. Mutations can change the sequencing of tumour suppressor genes and oncogenes, and hence their function. As a result, XP patients have a significantly increased risk of acquiring skin cancer, as well as a >10- to 20-fold increased risk of internal malignancies such as leukemias, brain tumors, and lung tumors before the age of 20 (49). Mutations can result from the bypass of unfixed DNA lesions while replication in proliferating cells of XP patients. Mutations can change the sequencing of tumour suppressor genes and oncogenes, and hence their function. As a result, XP patients have a significantly increased risk of acquiring skin cancer, as well as a >10- to 20-fold increased risk of internal malignancies such as leukemias, brain tumors, and lung tumors before the age of 20.

Patients with XP have different sunburn reactions that are inversely related to cancer risk: 60% of cases exhibit severe UV light sensitivity from birth, whereas the remaining 40% only show obvious indications around the age of two years, when a freckle-like pigmentation appears on the face. Surprisingly, the latter had a higher risk of developing cancer. Patients with XP can also have neurological problems in 20–30% of instances (50).

Ataxia Telangiectasia The two serine-threonine kinases ATM (ataxia telangiectasia (AT) mutated) and ATR (ATM and RAD3-related), which both belong to the phosphonositide 3-kinase (PI3K)-related protein kinases (PIKKs) family, along with SMG-1 (mutagenesis suppressor in genitalia), DNA-PKcs (DNA dependent protein kinaskinase catalytic subunit) and mTOR (mammalian target of rapamycin).

CONCLUSION

Aging is caused by the buildup of damage in several cellular elements, with DNA damage being one of the most important. Thousands of insults to DNA occur every day, either due to endogenous factors (such as metabolism) or exogenous factors (such as contact with radiation sources or exposure to toxic substances); however, only a small percentage (less than 0.02 percent) accumulates as permanent damage, with the rest being completely repaired. However, if only one gene is not repaired and its function is important as that of a proto-oncogene, a tumor suppressor, or any DNA repair genes, this could lead to accumulation of mutations, and then DNA damage checkpoints can halt the cell cycle and induce cellular senescence or apoptosis, or well erroneous repair or replicative bypass of lesions can result in mutations and chromosomal aberrations leading the cells to transform into cancer cells. Overall, this area needs to be more exploited in order to improve our quality of life and prevent or delay the harmful effects of aging. Thus, the more knowledge we acquire about the natural cell aging process and its interrelation with the mechanisms of DNA repair, the closer we will be to develop drugs, therapies, or even vaccines that could help us to prolong our life.

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