Review Article

Role of DNA Repair Pathways in Aging- A Review

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ABSTRACT

Aging is a process where decrease of function occurs followed by DNA damage. DNA replication or transcription are affected because of structural damage to DNA, which leads to alteration or elimination of fundamental cellular process. To overcome this defect cell develop certain repair mechanisms. They are Base Excision Repair, mismatch repair, nucleotide excision repair, and double-strand break repair, homologous recombination, non-homologous end joining. Cancer cells can have increased rate of proliferation capacity, reduced apoptosis and increased capacity to invade basement membrane and metastasize. Because of genomic instability of cancer cell they easily break and reform chromosome and stimulate fusion of new oncogene and tumor suppressor gene are inactivated. To overcome this cancer cells should have capacity to withstand DNA damage.

Key Words: DNA, Aging, Repair pathways.

Introduction

Aging can be defined as progressive decline in function and increase in mortality over a period of time. DNA is considered as precious molecule as it helps in encoding information about cellular contents. If chromosome is lost it is difficult to replace it and because of its irreplaceable nature, it makes itself as a critical target especially to the damage that occurs during aging.DNA damage if not corrected prior to replication it results in cytotoxic development[1]. Hence DNA replication should be checked properly in cell cycle. DNA damage can occur because of external and internal sources. The external sources are the ionizing radiation and genotoxic drugs and internal sources includes the replication errors, spontaneous chemical changes to DNA programmed double-strand breaks also DNA damaging agents that are normally present in the cells such as reactive oxygen species, super -oxide anion, hydroxyl radical, hydrogen peroxide. ROS cause lipid peroxidation, protein damage and many DNA lesions. This ROS cause persistent damage to cell further which pave way for DNA damage.[1]

DNA Repair Pathways in Aging

MISMATCH REPAIR

Mispaired bases occur because of replication errors, recombination of imperfectly matched sequences and deamination of 5-methyl cytosine. Role of mismatch repair is to remove this Mispaired bases. DNA replication that had overcome this point mutation occur when DNA replication cross a mismatched base repair. Mismatch repair found to play a role in repairing oxidative damage[2].

Mismatch repair (MMR) is needed for the maintenance of repeated sequence. Mutation in MMR genes leads to destabilization of microsatellites, which in turn causes this microsatellite instability to increases with age. In a study, when cells that are of different passages treated with mismatch –inducing agent and when detected using alkaline comet assay, they found MMR declined as age increases. Thus age related alteration occurs in mismatch repair.

Mismatch repair play role in correcting mutations associated with DNA replication. Microsatellite instability occurs because of missing gene or mutation of MSH2, MSH6 or PMS2 gene and this dysfunction is found to be associated with hereditary non-polyposis colon Cancer[3].

Base Excision Repair

Lesions that affect only one DNA strand is removed by excision repair and complementary strand fill the gap. Base excision repair (BER) repairs minimal alteration in DNA such as oxidized bases or incorporation of uracil which will not distort overall structure of DNA helix. Damage that are induced by reactive oxygen species is corrected by BER. Excision repair is classified as short patch base excision repair, in which one nucleotide is replaced, whereas in long patch where 2-23 nucleotides are replaced[4].

DNA glycosylaes initiates BER, that in turn cleave N-glycosylaes BER, that in turn cleave N-glycosylic bond of damaged bases sparing apurinic/ apyrimidinic site. AP endonucleases process abonic site leaving single stranded gap. This gap is then filled by DNA polymerases beta and ligated by DNA ligase.[4]

The levels and kinetics of AP site, after DNA damage in nuclear DNA revealed that higher basal level of AP in senescent human fibroblast and leukocytes compared to young cells. Deficiency in DNA glycosal activity was found in old cells, when treated with H_2O_2 or MMS, as the level of AP site increase in younger cells when compared to old cells. When oxidized guanine was measured after exposure to gamma radiation the level was increased, because of BER enzyme activity is altered followed by altered response to DNA damage. In younger mice expression of DNA polymerase and AP endonuclease found to be induced by DNA damage to young mice, whereas in aged mice there is lack of inducibiity.

There was deficient in translocation of oxoguanie DNA glycosylase and AP endonuclease in to both nuclei and mitochondria of old mice and senescent human fibroblast. Efficiency of BER is sequence-specific where their gene expression is down regulated with age when compared with young individuals[5].

Nuceotide Excision Repair

DNA oligo nucleotides that contains damaged base is removed by nucleotide excision repair(NER). The bulky lesions that are caused by carcinogenic compound, covalent linkages between adjacent pyrimidine as a result of UV exposure is recognized by NER. Nucleotide excision repair is classified as global genome repair which has been found to occur everywhere in genome and transcription coupled repair that removes lesions in transcribed strand. Damage in XPC-HR23B is recognized by GG-NER damage, further verified by XPA. XPB, XPD, helicases in complex with TF11H basal transcription initiation factor, unwound DNA and further incision is made in XPF and XPG damage strand. DNA polymerase and DNA ligase remove and repair damaged strands. Repair process is initiated by TCR pathway stabled RNA-POIII along with TCR specific proteins and CSB and CSA.[6]

In a study they measured the disappearance of cyclobutane pyrimidine dimers from genomic DNA in human fibroblast by treating the cells with UV and genomic DNA is removed and incubated with T4 endonuclease, which cleave priymide dimmers of DNA. Restriction enzymes cleave the DNA, that is separated on a alkaline gel and intensity of band to specific gene is determined by southern hybridization.[6] They found nucleotide excision repair activity decreased in old or senescent individuals.

Double Strand Break

Most lethal of all DNA lesions is double strand break. In unrepaired double strand break (DSB) chromosome segments is lost and affects survival of cell. DSBs destabilize the genome and cause genomic rearrangements if its misrepaired[7]. Deregulation of transcription and malignancies occur because of genomic rearrangement which is common in aging. Homologous recombination and Non-homologous end rejoining (NHEJ) repair Double strand break in DNA . HR mediated repair of DSB occur in template of sister chromatid which is used to copy missing information in to broken locus. RAD52 mediates repair by HR along RAD52 group. DNA damage can be repaired without genetic consequences as sister chromatids are similar to each other, whereas NHEJ fuses two broken ends without regard for sequence homology. KU70/KU80 hetero dimer along with NHEJ binds with broken DNA ends. Artemis –DNA PKAS complex are recruited by KU and prepare them for ligation. When DNA polymerase of POLX fill the gap by ligase forms a complex leading to deletion or insertion of filler DNA. Single strand annealing can repair double strand break between two direct repeats which is a mutagenic, mechanism in which sequence between the repeats is deleted. As cancer is associated with genomic rearrangements and loss of Increase in heterozygosity, incidence of cancer is found to be first indication of age-related changes in DSB repair [8].

In a study they found age related decline in efficiency of rejoining x-ray induced DNA breaks in lymphocytes that are normal in humans. When genes involved in DSB repair are disrupted it leads to premature aging phenotype. DSB repair were found to be less efficient during normal aging, the same pathway will also contribute in subtle way in onset of aged phenotype.[9-10]

Conclusion

All the pathways become less efficient with age, leading to mutation accumulation. The reason of DNA repair enzyme to get decreased with aging is because of DNA repair and DNA damage. When alteration in this response occur it leads to DNA damage. Another mechanism apoptosis which is triggered by DNA damage is down regulated in aging or senescence in turn altering p53

activity. Beyond DNA damage response old organisms are sensitive to stress leading to alterations, mutations in DNA repair gene which is the main reason for premature aging syndrome, therefore it is assumed that normal aging is caused as a part of decline in DNA repair capacity.

Imbalance between cell death and cell renewable leads to exhaustion of stem cell pool. Loss of tissue cellularity and declined function is main reason for accelerated aging. Also DNA damage and mutation may alter chromatin structure and cause epigenetic changes. Thus there is no reason why DNA repair cannot be improved. To conclude more research to be needed on mechanism of age-related changes in DNA repair, which will help us to up-regulate DNA repair and prevent further delay in aging and cancer.

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