Ramya /J. Pharm. Sci. & Res. Vol.5(11), 2013, 213 - 215

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

DNA REPAIR

Ramya Chellammal Muthusamy

Saveetha Dental College,Tamil Nadu

Abstract
The human genome, comprises about three billion base pairs coding for 40 000–50 000 genes and is constantly attacked byReactive metabolites, drugs and a environmental mutagens that affects its integrity. Thus it is obvious that continuous surveillance is necessary. This is where DNA repair mechanisms play a role, it Has evolved to remove or tolerate pre-cytotoxic and pre-mutagenic DNA lesions in an error-free method. Defects in DNA repair may be responsible for hypersensitivity to DNA-damaging agents, accumulation of mutations in the genome and to the development of cancer and various disorders. The importance of DNA repair is through DNA repair deficiency and syndromes, which are increased cancer incidence and multiple metabolic changes in DNA. Up to 135 genes have been found to be in association with DNA repair in humans. This review is aimed at updating our current knowledge in DNA-repair genes and the related proteins, participating either directly in DNA repair, or in signaling of DNA damage.

Keywords
DNA repair, proteins, mutations, DNA damaging

INTRODUCTION

DNA repair is a collection of processes by which a cell identifies and corrects damage to the DNA molecules that encode its genome. In human cells, both normal metabolic activities and environmental factors such as UV light and radiation can cause DNA damage, resulting in as many as 1 million individual molecular lesions per cell per day **[1]** These can cause structural damage to the DNA molecule and can alter the cell's ability to transcribe the gene that the affected DNA encodes. Other lesions induce potentially harmful mutations in the cell's genome, which affect the survival of its daughter cells after it undergoes mitosis. As a consequence, the DNA repair process is constantly active as it responds to damage in the DNA structure. When normal repair processes fail, and when cellular apoptosis does not occur, irreparable DNA damage may occur, including double-strand breaks and DNA cross-linkages **[2][3]**. The DNA repair ability of a cell is to ensure the integrity of its genome and thus required for its normal functioning for the organism. Many genes which influence life span of an individual have turned out to be involved in DNA damage repair and protection **[4]**. The primary structure of the DNA molecule is the one which is vastly affected; that is, the bases get chemically modified. These modifications can alter the molecules' regular helical structure by introducing nonsense chemical bonds or bulky adducts that do not fit in the usual standard double helix. Unlike proteins and RNA, DNA usually lacks tertiary structure and therefore no damage occurs at this level. DNA in erythrocytes is found to be highly coiled and is referred to as ‘histones’ through packaging and are highly vulnerable to damage. When replication of damaged DNA occurs before cell division this can lead to addition of wrong bases, daughter cells which inherit these bases carry mutations which are not required. Also the original DNA sequence cannot be recovered.

SOURCES OF DNA DAMAGE:

Endogenous- are produced by normal metabolic activities

Exogenous- are caused by external agents:

- UV radiation
- Viruses
- Plant toxins
- hydrolysis

TYPES OF DNA DAMAGE:

Endogenous and Exogenous-Ionizing radiation such as that created by radioactive decay or in cosmic rays causes breaks in DNA strands. Low-level ionizing radiation may induce irreparable DNA damage (leading to replicational and transcriptional errors needed for neoplasia or may trigger viral interactions) leading to pre-mature aging and cancer**[5][6][7]**.

Thermal disruption at elevated temperature increases the rate of depurination (loss of purine bases from the DNA backbone) and single-strand breaks. For example, hydrolytic depurination is seen in the thermophilic bacteria, which grow in hot springs at 40-80 °C**[8][9]**.

UV damage, alkylation/methylation, X-ray damage and oxidative damage are examples of induced damage. Spontaneous damage can include the loss of a base, deamination, sugar ring puckering and tautomeric shift **[10]**

DNA REPAIR MECHANISIMS

The plethora of DNA damages is repaired by specialized processes (as depicted in Figure 1). Direct reversal (DR) is mostly used in the repair of alkylated bases. The major advantage of DR is that it does not need sequence information to repair. Two DR mechanisms exist:1) suicidal methyltransferases that transfer the methyl group from the DNA to a cysteine residue in the transferase itself, and 2) a newly identified AlkB family of dioxygenases that directly reverse the damage by oxidative demethyla□on **[12].** Base excision repair (BER) is responsible for repair of the most common lesions. Shortpatch BER removes the damaged base and replaces it, using the complementary strand as a template **[13].** Long-patch BER works via a similar mechanism and differs in the fact that it involves the removal of a few bases instead of just one. This mechanism is used in the repair of single-strand breaks **[11].** It is anticipated that detailed understanding of the DNA repair mechanisms will lead to insights for prevention of diseases, for diagnosis, into resistance to chemotherapeutic agents, and for development of therapeutic tools. This chapter briefly summarizes the known DNA repair pathways and reviews the approaches for clarifying and measuring DNA repair in vivo and in vitro.Excellent comprehensive reviews have recently been published on repair mechanisms and chromatin structure **[14, 15],**on the chemistry and biology of DNA repair **[16],** on the chemistry of glycosylases **[17],** and on how DNA repair mechanisms may relate to cancer and ageing **[18].** In this chapter we also describe the current available methods for estimation of DNA repair,qualitatively and quantitatively.

DNA REPAIR SYNDROMES

During evolution several DNA repair pathways have emerged **[19]** . Most of the repair mechanisms have been strongly conserved during evolution, with evident parallels between human and yeast and even Eschericia coli. In only a few cases have species specific repair systems evolved.

The most relevant repair mechanisms are:

1) Direct reversal of damage
2) Base excision repair
3) Nucleotide excision repair
4) mismatch repair
5) Recombination repair and
6) Post replication repair. **[20].**

The first evidence that DNA repair plays an important role in tumour prevention was reported more than 25 years ago, by Cleaver [**21**]. He showed that the cancer-prone hereditary disorder xeroderma pigmentosum (XP), has as its bases on a defective nucleotide gxcision repair (NER) pathway. This rare, autosomal recessive disorder is characterized by extreme sensitivity of affected individuals to UV-light (resulting in DNA damage), in addition to a predisposition to the development of skin-cancer **[22].** In addition to this prototype repair disorder, other cancer-prone syndromes based on a defect in one of the repair processes, other than NER, are known. Examples are: Fanconi's anaemia (FA) and Bloom syndrome (BS).

REFERENCES

1. a b Lodish H, Berk A, Matsudaira P, Kaiser CA, Krieger M, Scott MP, Zipursky SL, Darnell J. (2004). Molecular Biology of the Cell, p963. WH Freeman: New York, NY. 5th ed.
2. a b Acharya, PV (1971). "The isolation and partial characterization of age-correlated oligo-deoxyribo-ribonucleotides with covalently linked aspartyl-glutamyl polypeptides.". Johns Hopkins medical journal. Supplement (1): 254–60. PMID 5055816. ^
3. a b Bjorksten, J; Acharya, PV; Ashman, S; Wetlaufer, DB (1971). "Gerogenic fractions in the tritiated rat.". Journal of the American Geriatrics Society 19 (7): 561–74. PMID 5106728. ^
4. Browner, WS; Kahn, AJ; Ziv, E; Reiner, AP; Oshima, J; Cawthon, RM; Hsueh, WC; Cummings, SR. (2004). "The genetics of human longevity". Am J Med 117 (11): 851–60. doi:10.1016/j.amjmed.2004.06.033. PMID 15589490.
5. Acharya, PVN;The Effect of Ionizing Radiation on the Formation of Age-Correlated Oligo Deoxyribo Nucleo Phospheryl Peptides in Mammalian Cells; 10th International Congress of Gerontology, Jerusalem. Abstract No. 1; January 1975. Work done while employed by Dept. of Pathology, University of Wisconsin, Madison. ^
6. Acharya, PVN; Implicatons of The Action of Low-Level Ionizing Radiation on the Inducement of Irreparable DNA Damage Leading to Mammalian Aging and Chemical Carcinogenesis.; 10th International Congress of Biochemistry, Hamburg, Germany. Abstract No. 01-1-079; July 1976. Work done while employed by Dept. of Pathology, University of Wisconsin, Madison. ^
7. Acharya, PV Narasimh; Irreparable DNA-Damage by Industrial Pollutants in Pre-mature Aging, Chemical Carcinogenesis and Cardiac Hypertrophy: Experiments and Theory; 1st International Meeting of Heads of Clinical Biochemistry Laboratories, Jerusalem, Israel. April 1977. Work conducted at Industrial Safety Institute and Behavioral Cybernetics Laboratory, University of Wisconsin, Madison. ^
8. Madigan MT, Martino JM (2006). Brock Biology of Microorganisms (11th ed.). Pearson. p.136. ISBN 0-13-196893-9.
9. Ohta, Toshihiro; Shin-ichi, Tokishita; Mochizuki, Kayo; Kawase, Jun; Sakahira, Masahide; Yamagata, Hideo (2006). "UV Sensitivity and Mutagenesis of the Extremely Thermophilic Eubacterium Thermus thermophilus HB27". Genes and Environment 28 (2): 56–61. doi:10.3123/jemsge.28.56.
10. DNA Lesions That Require Repair: http://www.ncbi.nlm.nih.gov/books/bv.fcgi?highlight=lesion&rid=mcb.table.3236
11. Hoeijmakers, J.H. (2001). Genome maintenance mechanisms for preven□ng cancer. Nature 411, 366-374.
12. Nordstrand, L.M., Ringvoll, J., Larsen, E., and Klungland, A. (2007). Genome instability and DNA damage accumula□on in gene-targeted mice. Neuroscience 145, 1309-1317.
13. Wilson, D.M., 3rd, and Bohr, V.A. (2007). The mechanics of base excision repair, and its relationship to aging and disease. DNA Repair (Amst) 6, 544-559. genetic diseases. Prog Nucleic Acid Res Mol Bio 63:257–310
15. Wilson DM, III, Sofinowski TM,McNeill DR (2003) Repair mechanisms for oxidative DNA damage. Front Biosci 8:d963–d981

16. Schärer OD (2003) Chemistry and biology of DNA repair. Angew Chem Int Ed Engl 42:2946–74
17. Stivers JT, Jiang YL (2003) A mechanistic perspective on the chemistry of DNA repair glycosylases. Chem Rev 103:2729–59
18. Hoeijmakers JH (2001) Genome maintenance mechanisms for preventing cancer. Nature 411:366–74
19. Friedberg, E.e., C.e. Walker and W. Siede. 1995. DNA repair and mutagenesis. ASM Press, Washington D.C.
20. Frederick, C.D., R.H. Amirkhan, R,A. Schultz and E.e. Friedberg. 1994, Structural and mutational analysis of the xeroderma pigmentosum group D (XPD) gene. Human Molecular Genetics 3: 1783-1788.
21. Cleaver, J.E. 1968. Defective repair replication in xeroderma pigmentosum. Nature 218:652-656.
22. Cleaver, J.E. and K.H. Kraemer, 1994. Xeroderma Pigmentosum and Cockayne syndrome. p. In Scriver, C.R., A.l. Beaudet, W.S. Sly, D. Valle (ed,), The metabolic basis of inherited disease. Seventh edition, McGraw-Hili Book Co., New York.