Mitochondrion xxx (2013) xxx–xxx

Contents lists available at ScienceDirect

Mitochondrion

journal homepage: www.elsevier.com/locate/mito

Review

A short review on the implications of base excision repair pathway for neurons: Relevance to neurodegenerative diseases

Anil K. Mantha [a,b,*], Bibekananda Sarkar [a], Gianluca Tell [c]

[a] Center for Biosciences, School of Basic and Applied Sciences, Central University of Punjab, Bathinda 151 001, Punjab, India
[b] Department of Biochemistry and Molecular Biology, University of Texas Medical Branch, Galveston, TX 77555, USA
[c] Department of Medical and Biological Sciences, University of Udine, 33100 Udine, Italy

ARTICLE INFO

Article history:
Received 7 August 2013
received in revised form 31 October 2013
accepted 31 October 2013
Available online xxxx

Keywords:
Oxidative stress
DNA glycosylase
Base excision repair
Single-strand break repair
AP endonuclease 1
Neurodegenerative disorders
Reactive oxygen/nitrogen species (ROS/RNS)

ABSTRACT

Oxidative DNA damage results from the attack by reactive oxygen and nitrogen species (ROS/RNS) on human genome. This includes base modifications such as oxidized bases, abasic (AP) sites, and single-strand breaks (SSBs), all of which are repaired by the base excision repair (BER) pathway, one among the six known repair pathways. BER-pathway in mammalian cells involves several evolutionarily conserved proteins and is also linked to genome replication and transcription. The BER-pathway enzymes, namely, DNA glycosylases (DGs) and the end-processing proteins such as abasic endonuclease (APE1), form complexes with downstream repair enzymes via protein–protein and DNA–protein interactions. An emerging concept for BER proteins is their involvement in non-canonical functions associated to RNA metabolism, which is opening new interesting perspectives. Various mechanisms that are underlined in maintaining neuronal cell genome integrity are identified, but are inconclusive in providing protection against oxidative damage in neurodegenerative disorders, main emphasis is given towards the role played by the proteins of BER-pathway that is discussed. In addition, mechanisms of action of BER-pathway in nuclear vs. mitochondria as well as the non-canonical functions are discussed in connection to human neurodegenerative diseases.

Contents

Abbreviations: AD, Alzheimer's disease; AP site, apurinic/apyrimidinic site; APE1, apurinic/apyrimidinic endonuclease 1; Aβ, amyloid beta; BER, base excision repair; CaMKII, Ca^{2+}/Calmodulin-Dependent Protein Kinase II; CDK, cyclin-dependent kinase; CREB, cAMP response element-binding; IP, immunoprecipitate; NFT, neurofibrillary tangles; PARP-1, poly [ADP-ribose] polymerase 1; Ref-1, redox effector factor-1; SSBR, single-strand break repair; SSBs, single-strand breaks; TF, transcription factor; MGMT, O^6-methylguanine DNA methyltransferase; NER, nucleotide excision repair; NHEJ, nonhomologous end joining; XP, Xeroderma pigmentosum; CS, Cockayne syndrome; TTD, trichothiodystrophy; CNS, central nervous system; GEN1, gap endonuclease; XRCC1, X-ray repair cross-complementing 1; PCNA, proliferating cell nuclear antigen; RPA, replication protein A; DG, DNA glycosylase; PNKP, polynucleotide kinase 3′-phosphatese; ROS/RNS, reactive oxygen species/reactive nitrogen species; UV-A, ultraviolet ray-A; ND, neurodegenerative disease; mtDNA, mitochondrial DNA; nuDNA, nuclear DNA; FEN, flap endonuclease; TDG, thymine-DNA glycosylase; OGG1, 8-oxoguanine glycosylase; NEIL1, endonuclease VIII-like 1; UDG1, uracil-DNA glycosylases; SN-BER, short patch-base excision repair; LP-BER, long patch-base excision repair; HhH, helix-hairpin-helix; MUTYH, mutY homolog *E. coli*; MPG, 3-methyladenine-DNA glycosylase; BRCT, BRCA1 C-terminus; BBB, blood–brain barrier; MMS, methyl methanesulfonate.

* Corresponding author at: Center for Biosciences, School of Basic and Applied Sciences, Central University of Punjab, Bathinda 151 001, Punjab, India.
E-mail addresses: anilmantha@gmail.com, Anil.kumar@cup.ac.in (A.K. Mantha).

1567-7249/$ – see front matter
http://dx.doi.org/10.1016/j.mito.2013.10.007

1. Introduction

DNA damage is balanced with repair in a homeostatic process, and when damage exceeds the repair, final outcome may be cell cycle arrest, apoptosis or genome mutation. DNA damage occurs due to various external and internal causes. In neuronal cells, most of the DNA damage is repaired by the base excision repair (BER) pathway, as neuronal cells are partially differentiated cells and replication derived repair is not possible in these cells. It is very important to study the mechanisms and enzymes involved in BER-pathway for neuronal survival. In neuronal cells, the role of different proteins in BER-pathway in both nucleus and mitochondria is not fully elucidated, yet.

2. Roles of base excision repair in oxidative DNA damage repair

Mammalian cells are constantly exposed to stress from external and internal agents. Oxidative stress is a common feature of all stresses, and to maintain cellular integrity, mammalian cells have evolved different repair mechanisms. Various chemical events may lead to DNA damage including hydrolysis and exposure to reactive oxygen substances (Nilsen et al., 2000) and other reactive metabolites (Bergamini et al., 2004). In normal dividing cells, the DNA damage is sensed through different cell cycle checkpoints, and if DNA damage occurs before cell division then cell division stops in order to repair the damage (Houtgraaf et al., 2006). DNA repair and its mechanism in neurons are one of the less studied area. DNA damage repair mechanisms in neuronal cells are different, as neurons are in postmitotic stage and not able to divide (Fishel et al., 2007; Nouspikel and Hanawalt, 2002). The repair mechanisms in neuronal cells involve different pathways including: direct reversal (O^6-methylguanine DNA methyltransferase; MGMT), mismatch repair, double strand break (DSB) repair via homologous recombination (HR) and non-homologous end joining (NHEJ). The mismatch occurs due to wrong incorporation of bases and deamination of bases due to oxidative damage, but these repair mechanisms are not highly efficient in neurons as they are terminally divided cells and cell division is not possible in these cells (Kruman, 2004). Nucleotide excision repair (NER) was initially the main focus of research as most of the neuronal damage occurs due to the defect in NER (Hitomi et al., 2007). Xeroderma pigmentosum (XP), Cockayne syndrome (CS) and trichothiodystrophy (TTD) are the family of sunlight sensitive disease and caused by inefficiency in the components of the NER pathway (Laposa and Cleaver, 2001). BER is the primary nuclear and mitochondrial DNA repair pathway for small base modifications such as alkylation, deamination and oxidation, and is thought to play a critical role during development and maintenance of the central nervous system, CNS (Chen et al., 2000).

BER is the main repair pathway in postmitotic cells, in which simple base modifications are more likely to occur than major damages to DNA (Rao, 2007). BER is a repair pathway predominant for the processing of small base lesions, derived from oxidation and alkylating damage and genotoxic chemicals (Hegde et al., 2008). The overall estimate of 10^4 base damages/mammalian cells/day underlines the importance of BER (Lindahl, 1993). The BER pathway mainly requires four types of enzymes, DNA glycosylase, AP endonuclease, DNA polymerase and DNA ligases (Dantzer et al., 2000; Hegde et al., 2008, 2010). In addition, proteins like XRCC1, PCNA and RPA, are also required (Mitra et al., 2001). The basic BER reaction comprises three steps: (1) base lesion recognition and excision by a DNA glycosylase, followed by cleavage of the resulting apurinic/apyrimidinic (AP) site in a concerted reaction by the DG itself (for bifunctional DG) or by APE1 (for monofunctional DG) (Hegde et al., 2012; Kulkarni et al., 2008; Mitra et al., 2001; Pena-Diaz et al., 2012); (2) cleaning of 3′ blocked termini at the strand break by APE1 and/or polynucleotide kinase 3′ phosphatase (PNKP) and 5′ blocking phosphodeoxyribose by DNA polymerase-β (pol-β) and gap filling by a DNA polymerase; and (3) nick sealing by DNA ligase to complete the repair [Fig. 1] (Hegde et al., 2008, 2012). Notably, the enzymes involved in BER-pathway are highly conserved phylogenetically.

3. Sources of endogenous and exogenous DNA damage to neuronal cells

Damage to DNA can be induced by several chemical reactive species and physical agents or may occur spontaneously through intrinsic instability of chemical bonds in DNA (Table 1). Even under normal physiologic conditions, DNA is continuously being damaged (Altieri F Fau-Grillo et al., 2008). These attacks can be divided into two broad categories: exogenous and endogenous (Altieri F Fau-Grillo et al., 2008). Exogenous and environmental sources of oxidation relate to specific exposures of the organism to ionizing radiations like X, γ and cosmic rays. Apart from that, radon decay, oxidizing chemicals and UV-A solar light are also involved in these types of DNA damage (Branzei and Foiani, 2008). Brain constitutes around 2–3% of total body mass, but it utilizes 20% of body basal oxygen supply (Marlatt et al., 2004). Intracellular (endogenous) sources of oxidative stress are primarily produced by O_2 metabolism (electron transport chain), immune responses and inflammation (Lee and Wei, 2007). The result is production of reactive oxygen/nitrogen species (ROS/RNS) which react with the DNA and produce various lesions and adducts (Raffoul et al., 2012). DNA damage can be induced also in neighboring or distant cells via an inflammatory-based mechanism, and the first barrier defense is accomplished through different enzymatic antioxidants, which act as scavengers of free radicals (Lobo et al., 2010).

The occurrence of neurodegenerative disease is a slow, progressive and irreversible degeneration of neurons and synapse of selected areas of nervous system (Fitzner and Simons, 2010). Neurodegenerative diseases (NDs) are caused by multifactorial etiologic causes which include genetic, environmental or endogenous insults (Singh et al., 2013). NDs are classified according to genetic factors and the major depositing compounds, so NDs are also known as protein misfolding diseases or proteinopathies (Jellinger, 2010). In Alzheimer's and Parkinson's diseases (AD and PD), a large body of evidence shows damaged energy metabolism and around 50% reduction in mtRNA content and is likely to reduce oxidative phosphorylation (Jellinger, 2010). In PD, iron is deposited in the substantia nigra (SN), and increased iron deposits in the SN may have genetic and non-genetic causes (Gerlach et al., 2006). In PD brain, increased iron is often accompanied by decreased ferritin synthesis, resulting in free iron overload (Dexter et al., 1990). The Cu(II) in submicromolar and Fe(II/III) in micromolar concentrations specifically inhibit the NEILs and not OGG1 (Hegde et al., 2010). Both

Please cite this article as: Mantha, A.K., et al., A short review on the implications of base excision repair pathway for neurons: Relevance to neurodegenerative diseases, Mitochondrion (2013), http://dx.doi.org/10.1016/j.mito.2013.10.007