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Human NEIL1 DNA glycosylase: Structure, function and polymorphisms

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ABSTRACT

Our cells are continuously exposed to oxidative stress which produces oxidative lesions in DNA. These lesions are recognized and removed by glycosylases. NEIL1 glycosylase is present in mammalian cells that possess unique characteristic of removing lesions from wide type of structures like dsDNA, ssDNA, interstrand crosslinks, bubbles and bulges. Impairment in its activity severely affects the repair ability of cell and can lead to various diseases including cancer. Polymorphic variants of NEIL1 are found to affect its activity differently with different substrates. Thus, variants in distinct regions of the gene can alter the structure or expression of NEIL1 protein and may influence the development of diseases. Therefore, characterization of polymorphisms and their study in association with various diseases like cancer would help in determining the risk associated with respective disease and response of patients to environmental factors and therapies. In this review, we have summarized various studies related to the NEIL1 polymorphisms and their effect.

Contents

1. Introduction

Our genome is continually exposed to reactive oxygen species (ROS) produced by wide range of mechanisms, e.g., exogenous sources, ionizing radiations, ultraviolet radiations, chemotherapeutics, other harmful chemicals and endogenous sources such as by-products of aerobic metabolism, inflammation reactions, intermediates of metabolism and hormones (De Bont & van Larebeke, 2004). These ROS create oxidative stress which leads to several types (as many as 50,000) of lesions in DNA (Lomax et al., 2013). These lesions are genotoxic and/or mutagenic because they cause DNA strand break and base damage. Any of this damage can cause severe effect on genomic stability and can induce point or frameshift mutations. The ROS produced involve $O_2^{\bullet -}$ (superoxide radical anion), OH• (hydroxyl radical), singlet oxygen ($^1O_2$) and H_2O_2 (hydrogen peroxide) (De Bont & van Larebeke, 2004). OH• is the

Abbreviations: 8-oxoG, 8-dihydro-2′-deoxyguanosine; 5-OHU, 5-hydroxyuracil; AP, apurinic/apyrimidinic; BER, base excision repair; CCA, cholangiocarcinoma; DHU, 5,6 dihydrouracil; DSB, double-strand breaks; dRP, deoxyribose phosphate; Fapy-A, 4,6-diamino-5-formamidopyrimidine; Fapy-G, 2,6-diamino-4-hydroxy-5-formamidopyrimidine; FEN-1, flap-endonuclease 1; HhH, helix-hairpin-helix; KC, keratoconus; MeFapyG, methylated 2.6-diamino-4-hydroxy-5-formamidopyrimidine; MPG, 3-methylpurine DNA glycosylase; nsSNPs, non-synonymous single nucleotide polymorphisms; OGG1, 8-oxoguanine DNA glycosylase; PCNA, proliferating cell nuclear antigen; PNK, polynucleotide kinase; Polδ, DNA polymerase δ; PSC, Primary sclerosing cholangitis; RIET, radiation-induced esophageal toxicity; ROS, reactive oxygen species; RP, radiation pneumonitis; SCCOOP, squamous cell carcinomas of the oral cavity and oropharynx; SSB, single-strand breaks; Tg, 5, 6-thymine glycol; UNG, uracil glycosylase; WRN, Werner RecQ helicase.

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most harmful (highly reactive) type of ROS which is also generated during inflammatory response (Griendling et al., 2000). Major lesions produced by oxidative stress are 5.6 dihydrouracil (DHU), 5-hydroxyuracil (5-OHU), 5, 6-thymine glycol (Tg), 5-(hydroxymethyl)-2′-deoxyuridine, 5-formyl-2′-deoxyuridine, 4.6-diamino-5-formamidopyrimidine (Fapy-A) and 2.6-diamino-4-hydroxy-5-formamidopyrimidine (Fapy-G), 7.8-dihydro-8-oxoadenine (8-oxo-A), 8-dihydro-2′-deoxyguanosine (8-oxoG) and single-strand breaks (SSB) etc. (De Bont & van Larebeke, 2004; Lomax et al., 2013; Hegde et al., 2008; Jaruga et al., 2000). Only radiation produces around 850 pyrimidine lesions, 450 purine lesions, 1000 single-strand breaks (SSB) and 20–40 double-strand breaks (DSB)/cell/Gy (Cadet et al., 2008). These lesions generate spontaneous mutations in the genomic DNA, e.g., deamination of C to U or 5-OHU causes transition mutation (GC → AT) because U and 5-OHU both pair with adenine (A) and guanine (G) is oxidized to 8-oxoG which pairs with A that leads to GC → AT transversion mutation (Helbock et al., 1999; Shibutani et al., 1991). These mutations when produced spontaneously in genes essential for apoptosis, cell cycle, genome maintenance (DNA repair), tumor suppressor and oncogene can result in cancerogenesis or other diseases like rheumatoid arthritis, aging etc. (Lomax et al., 2013; Levine, 1997; Ames et al., 1993; Gotz et al., 1994; Lovell et al., 2000).

It is essential to maintain genome integrity and stability which is assaulted by oxidative stress. To perform this function, all human cells have well developed repair systems. Base excision repair (BER) system is the most effective pathway responsible to revert back lesions caused by oxidative stress. BER repairs variety of lesions, except double strand DNA (dsDNA) break, e.g., oxidized bases, apurinic/apyrimidinic (AP) sites and single strand breaks of DNA (Hegde et al., 2008; Friedberg et al., 2004). Very first step of this pathway is the most crucial step which involves excision of oxidatively damaged bases by DNA glycosylase enzymes (Fig. 1). These enzymes remove damaged base by breaking glycosidic bond between base and deoxyribose sugar moiety (Krokan et al., 1997). Next step includes cleavage of DNA backbone by AP endonuclease (APE) or polynucleotide kinase (PNK), or by intrinsic AP lyase activity of DNA glycosylases. APE generates 3′-OH and 5′ deoxyribose phosphate (dRP) end. Then polymerase β (Pol β) clears 5′ termini and incorporate appropriate base at the abasic (damaged base) site. In final step, ligase enzyme joins the nick and DNA damage gets repaired (Mitra et al., 1997; Sobol et al., 2000; Matsumoto & Kim, 1995; Tomkinson et al., 2001).

DNA glycosylases are key enzymes of this pathway which initiate the pathway. Many DNA glycosylases are reported to be present in human cells. These can be differentiated on the basis of their substrate affinity. The first BER enzyme *Escherichia coli* uracil glycosylase (UNG) was discovered by Tomas Lindahl. It removes deaminated cytosines and misincorporated uracils from DNA. In humans, two versions of UNG, UNG1 for nucleus and UNG2 for mitochondria are found. Primary role of UNG2 and one more enzyme SMUG1 is to remove 5-hydroxymethyluracil from DNA. UNG1 and SMUG1 belong to UDG super family. Thymines are removed from thymine:guanine mismatches that arise from deamination of methyl cytosine by two mismatch DNA glycosylases, TDG and MBD4 (MED1). TDG has a higher affinity for uracil than thymine and MBD4 removes uracil and thymine that are result of deamination of CpG and methylated CpG, respectively. TDG is also a member of UDG superfamily. All glycosylases belonging to UDG superfamily are monofunctional. Alkyladenine DNA glycosylase (AAG) also called 3-Methylpurine DNA glycosylase (MPG) has affinity for a larger number of alkylated bases including 3-methyladenine, guanines methylated at the N3 or N7 position, etheno adenine and guanine, hypoxanthine and 8-oxoguanine as well as other alkylated and oxidized DNA substrates. MPG/AAG is a monofunctional glycosylase. It consists of a single mixed α/β domain that makes it different from other glycosylases. 8-Oxoguanine paired to cytosine, FapyG and 8-oxoA are recognized and removed by 8-Oxoguanine DNA glycosylase (OGG1). OGG1 belongs to the HhH family of DNA glycosylases and is a

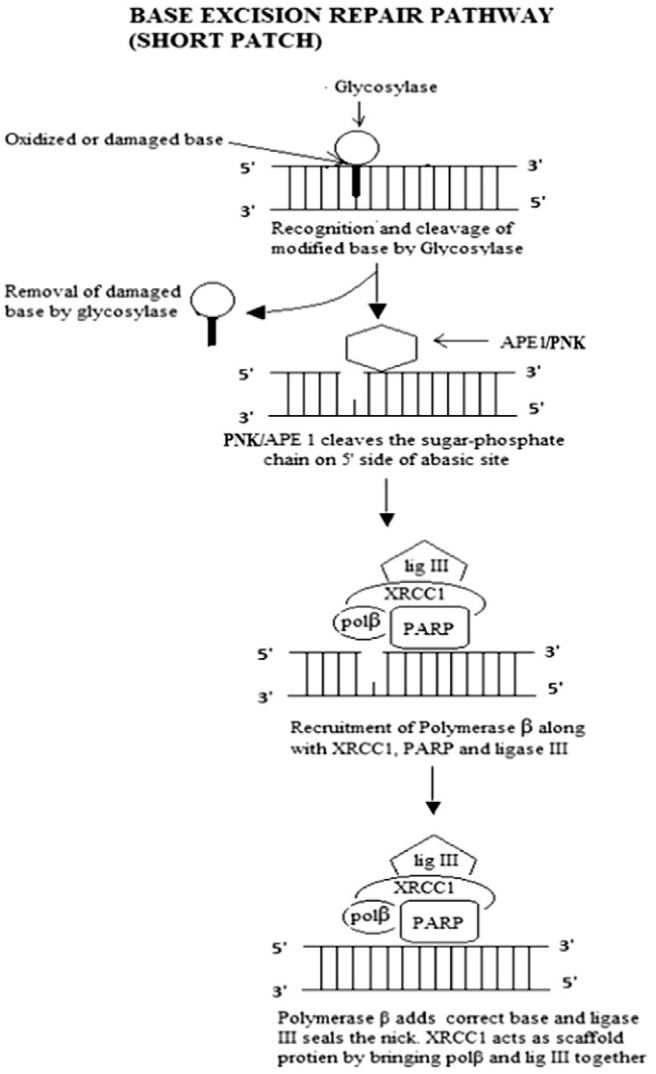

Fig. 1. BER pathway.

bifunctional glycosylase. It consists of GlyPro-rich loop and a conserved aspartic acid which initiates a nucleophilic attack on the ε-amino group of a conserved lysine. OGG1 is the only human glycosylase that efficiently removes 8-oxoG from DNA. If 8-oxoguanine (or FapyG) is stumble on by a replication fork before repair, adenine is often inserted opposite the base by the synthesizing polymerase. This adenine is recognized and removed by DNA glycosylase MUTYH. MUTYH also belongs to the helix-hairpin-helix (HhH) superfamily, along with HhH binding motif, it contains an iron sulfur cluster that is involved in DNA binding. It is a monofunctional glycosylase. MUTYH is the only glycosylase that removes adenine incorporated opposite 8-oxoG, although is also removed by the mismatch repair system (Fromme & Verdine, 2004; Grin & Zharkov, 2011; Nash et al., 1996; Wallace et al., 2012).

Oxidized pyrimidines and formamidopyrimidines are recognized and removed by other four DNA glycosylases. Human NTH1 (belonging to nth family of *E. coli*) seems to be a housekeeping DNA glycosylase that scans the DNA for these damages. NTH1, like MUTYH contains an iron sulfur cluster and HhH motif. It recognizes a broad spectrum of oxidized pyrimidines (De Bont & van Larebeke, 2004; Hegde et al., 2008; Fromme & Verdine, 2004; Grin & Zharkov, 2011; Nash et al., 1996; Wallace et al., 2012). In contrast to NTH1, the NEIL proteins seems to have specialized functions.NEIL1, NEIL2 and NEIL3 are newly identified DNA glycosylases. These were identified, characterized and named NEIL (Nei like) in 2002 by Hazara and colleagues (Hazra et al., 2002a; Hazra et al., 2002b). These belong to nei family of glycosylase because of