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Review

Gene susceptibility to oxidative damage: From single nucleotide polymorphisms to function

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ABSTRACT

Oxidative damage to DNA can cause mutations, and mutations can lead to cancer. DNA repair of oxidative damage should therefore play a pivotal role in defending humans against cancer. This is exemplified by the increased risk of colorectal cancer of patients with germ-line mutations of the oxidative damage DNA glycosylase MUTYH. In contrast to germ-line mutations in DNA repair genes, which cause a strong deficiency in DNA repair activity in all cell types, the role of single nucleotide polymorphisms (SNPs) in sporadic cancer is unclear also because deficiencies in DNA repair, if any, are expected to be much milder. Further slowing down progress are the paucity of accurate and reproducible functional assays and poor epidemiological design of many studies. This review will focus on the most common and widely studied SNPs of oxidative DNA damage repair proteins trying to bridge the information available on biochemical and structural features of the repair proteins with the functional effects of these variants and their potential impact on the pathogenesis of disease.

Contents

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1. Introduction

Radical oxygen species (ROS) are highly reactive oxidants which can be produced both endogenously, during normal aerobic cellular metabolism, and exogenously, by agents such as ionizing radiation, chemotherapeutic drugs and transition metals. A significant consequence of ROS production is damage to macromolecules, including induction of DNA base and sugar damage, abasic sites, DNA–protein cross-links and strand breaks, which can then lead to genomic instability [1]. Only few examples of a causal relation between oxidative stress and specific disease onset and progression exist (*e.g.* abetalipoproteinemia, Wilson's disease and thalassemia). For most of human diseases, such as chronic inflammatory, cardiovascular and neurodegenerative diseases, cancer and the aging process, an increased oxidative damage was measured in nucleic acids or proteins, but the causal role of oxidative stress in the pathogenesis and/or progression of disease remains to be clearly understood [2].

The first line of defense against ROS is the cellular antioxidant system. Once ROS reach DNA, multiple pathways that include DNA repair, cell cycle arrest and apoptosis provide a further protection level. DNA repair efficiently counteracts oxidative damage induced mutagenesis, cytostasis and cytotoxicity. In the nucleus, oxidative DNA lesions are repaired preferentially by base excision repair (BER) but also by nucleotide excision repair (NER), mismatch repair (MMR) and recombination [3]. Mitochondria, that are the main site for the production of ROS and also their main cellular target, are proficient in BER but not in NER [4].

There is only one example of a genetic disease caused by mutations in oxidative DNA damage repair genes, the MutY homolog (*Escherichia coli*) (MUTYH)-associated polyposis. Germline mutations in the DNA glycosylase MUTYH are associated with increased colon cancer risk [5]. There is also one report of metabolic syndrome resulting from knockout of the NEIL1 DNA glycosylase in a mouse model [6] but confirmatory data are required to strengthen this observation. It is likely that mutations in other genes of oxidative damage response are counter-selected, since the integrity of this pathway is required for protection from endogenous DNA damage. It is well accepted that the genetic predisposition to disease in the general population acts via combination of high-risk variants in a set of low and medium-penetrance genes [7]. Several epidemiological studies have shown an association between single nucleotide polymorphisms (SNPs) in DNA repair genes and increased sensitivity to mutagens or increased risk of disease (mostly cancer) but often with inconsistent results [8–10]. It should be considered that the limited number of SNPs usually analyzed in these studies might be a serious drawback when addressing a multigenic defect such as cancer and, more in general, complex diseases. Another key issue that is often neglected is the lack of functional studies for most of the SNPs commonly investigated.

In this study key proteins of oxidative DNA damage repair, namely 8-oxoguanine-DNA-glycosylase (OGG1), Nei-like protein 1 (NEIL1) and 2 (NEIL2), MUTYH, AP endonuclease 1 (APE1), X-ray cross-complementing group 1 (XRCC1), DNA polymerase β (POL β) and poly(ADP-ribose) polymerase-1 (PARP1) were selected and the information available on their mechanism of action was reviewed in relation to the functional effects of the most studied SNPs. Given the plethora of reports (often contradictory) describing pathological conditions associated with SNPs in oxidative DNA damage repair genes, only meta-analysis or large size epidemiological studies will be reviewed and the extent to which the functional significance of these variants may impact on the pathogenesis of disease will be critically addressed. The SNPs reviewed here are mostly non-synonymous SNPs (nsSNPs) that involve the alteration of the composition of the translated protein (by amino acid substitution or generation of truncated proteins). Evidence is emerging that SNPs in non-coding regions and even changes in wobble bases that do not affect amino acid sequence may be important as well. These SNPs are referred as synonymous SNPs (sSNPs).

2. OGG1

2.1. Structure and function

In mammals, the main DNA glycosylase for the removal of 8-oxoguanine (8OHG) paired with a cytosine is OGG1. In humans, OGG1 is able to efficiently remove 2,6-diamino-4-hydroxy-5-formamidopyrimidine (FapyG) when paired with cytosine also. Human *ogg1* gene consists of eight exons which can be alternatively spliced to produce different isoforms [11]. The most abundant mRNAs of OGG1 are type 1a and 2a. These two isoforms are ubiquitously expressed in human tissues. The type 1a mRNA arises from splicing of exon 8 and gives rise to the α-OGG1 protein, a 39 kDa enzyme mainly localized to nuclei [12] (Fig. 1). The type 2a mRNA contains the first six exons plus the exon 8 and codes for a 47 kDa protein, β-OGG1, which is exclusively localized to mitochondria [13].

The α-OGG1 protein has been extensively characterized both in the isolated form [14] and associated with DNA substrate [15]. It consists of three domains: the N-terminal domain (A domain) comprising several antiparallel β-sheet and two α-helices and the B and C domains that are mainly α-helical and are highly conserved among members of the DNA glycosylase/β-lyase family. The α-OGG1 and β-OGG1 isoforms share the same N-terminal domain, containing the mitochondrial targeting signal, but not the C-terminus [11]. Both isoforms contain two DNA binding motifs. The helix–hairpin–helix (HhH) motif is followed by a glycine/proline (Gly/Pro) loop and by a conserved aspartate and the Cys_2-His_2 zinc finger-like motif [16].

OGG1 is a bifunctional DNA glycosylase which excises the lesion via the N-glycosylic bond cleavage and then incises the resulting AP site in 3′ via a β-elimination reaction, leaving a 3′ α, β-unsaturated aldehyde and a 5′ phosphate. Through an active lysine residue located in the HhH region, OGG1 extrudes the 8OHG from the DNA substrate which is then inserted into the lesion recognition pocket. The 3′ phosphodiesterase activity of the major AP endonuclease, APE1, is required to remove the 3′ blocking group. Alternatively, APE1 can substitute the inefficient AP lyase activity of OGG1, by directly cleaving the generated AP site. It has been shown that APE1 is able to stimulate the AP lyase activity of OGG1, by preventing its reassociation to the AP site [17]. An inhibitory effect of the nucleosomal structure on OGG1 activity,

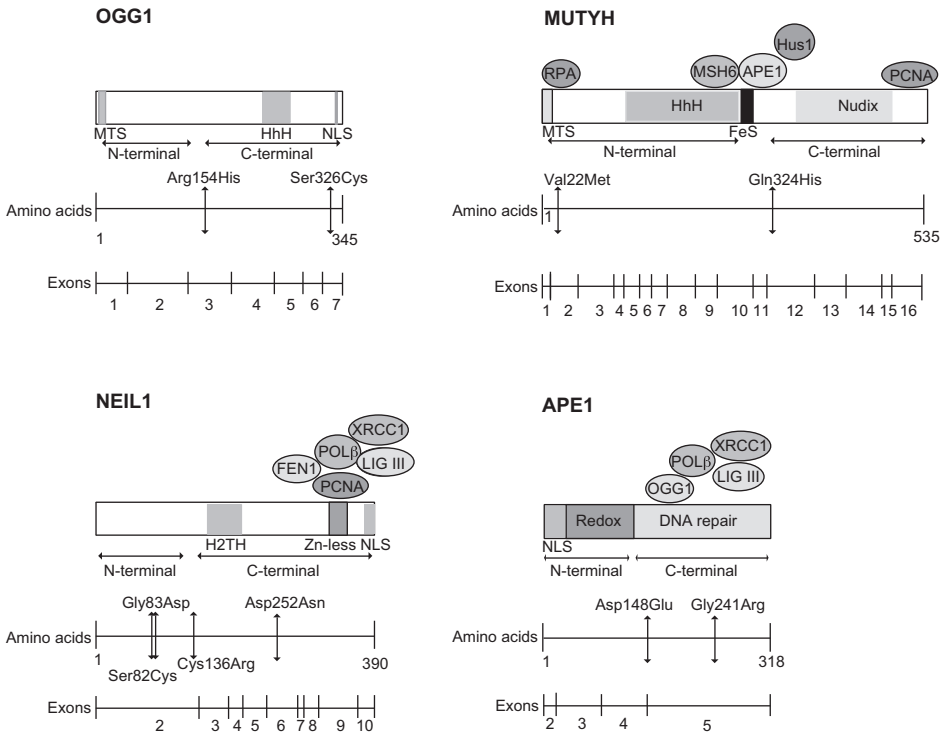

Fig. 1. α-OGG1, MUTYH, NEIL1 and APE1: protein and gene structure. The coding exons, the protein domains and the regions of interaction with other BER proteins are indicated. The location of the SNPs described in the text is reported.

as well as of other BER enzymes, has been reported. The addition of chromatin remodeling factors relieves OGG1 inhibition on chromatinized substrates. After oxidative stress the DNA glycosylase OGG1 is specifically recruited to euchromatin regions, leading to hypothesize that post-translational modifications of OGG1 and/or structural nuclear proteins could lead to an increase in their mutual affinity [18].

2.2. Relevant SNPs in this gene

The most studied *OGG1* SNP is the Ser326Cys (rs1052133) which derives from the serine residue substitution with a cysteine in the C-terminal domain (Fig. 1). The biochemical properties of this variant have not been fully clarified yet. Some lines of evidence suggest that the variant OGG1 is deficient in its catalytic activity and it is not stimulated by the presence of APE1 [19–21]. Moreover, it has been suggested that a change in the OGG1-Ser326Cys phosphorylation status would inhibit the variant localization to the nucleoli during the S-phase of the cell cycle [22]. It has been shown that lymphoblastoid cell lines established from individuals homozygous for the cysteine variant display increased micronuclei frequency and reduced 8OHG repair rates. The analysis of the redox status of the OGG1 protein *in vivo* has shown that the lower activity of OGG1-Cys326 is associated with the oxidation of Cys326 to form a disulfide bond [21]. Unfortunately, no clues on the function of this SNP can be drawn from the crystal structure of OGG1 [15] because none of them includes amino acids beyond position 325.

In a meta-analysis, an association between the Ser326Cys SNP and lung cancer risk has been reported [23]. Age-dependent CAG expansion in Huntington's disease has been shown to involve OGG1 [24] and interestingly an increased CAG expansion has been described in individuals with at least one copy of the mutant OGG1-Cys326 allele. These individuals tend to have a significant earlier onset of the disease [25]. Recently, the OGG1-Cys326 allele has been reported to be a risk factor for bladder cancer and for tumor recurrence in non-muscle invasive bladder cancer patients [26].

The Arg154His variant has been reported in a gastric cancer cell line [27]. This residue is involved in the recognition of cytosine opposite 8OHG as inferred form X-ray crystallography [15]. A recent molecular dynamics simulation study [28] has shown that this mutation causes conformational changes in the active site and in the recognition pocket. No data are currently available on its possible association with disease.

3. NEIL1

3.1. Structure and function

NEIL1 belongs to a class of DNA glycosylases homologous to the bacterial Fpg/Nei family, the Nei-like proteins (NEILs). The *NEIL1* gene contains ten exons and codes for a 43.7 kDa protein of 390 amino acids (Fig. 1). The structure of human NEIL1 has been solved by X-ray crystallography and is composed by two domains connected by a linker [29]. The N-terminal region contains the catalytic proline and a highly conserved lysine as proton donor, while the C-terminal comprises seven α-helices, two of which are involved in a helix–2-turns–helix (H2TH) motif, a signature for DNA binding. Two antiparallel β-strands following the α-helix form a structural motif mimicking an antiparallel β-hairpin zinc-finger (the zinc-less finger) that is typical of other proteins of Nei family. The importance of this motif for the DNA glycosylase activity of NEIL1 is testified by the reduced cleavage associated with a single amino acid substitution (Arg277Ala) in this 'zinc-less finger' motif [29].

NEIL1 is a bifunctional DNA glycosylase which exhibits a strong preference for excision of 4,6-diamino-5-formamidopyrimidine (FapyA) and FapyG from DNA with no significant specificity for 8-oxoG. This substrate specificity is distinct from that of OGG1 that efficiently excises FapyG and 8OHG, but not FapyA, from DNA

[30]. NEIL1 is also functionally distinct from OGG1 because of its high affinity for oxidized bases in single stranded and bubble DNA. This feature, together with the fact that NEIL1 interacts with DNA replication/repair factors (*i.e.* PCNA and FEN1) and increases during S-phase, led to hypothesize that the primary role of NEIL1 is in transcription and/or replication associated repair [31,32]. NEIL1 is also able to cleave oxidized pyrimidines such as thymine glycol, 5-hydroxycytosine (5OHC), dihydrothymine and dihydrouracil (5OHU). After base removal, NEIL1 cleaves the abasic site by a β–δ elimination mechanism, which requires the polynucleotide kinase (PNK) protein to generate the 3′OH terminus, thereby bypassing APE1. This generates an APE1-independent BER that may represent a redundant mechanism of defense against oxidative damage [33]. It has been reported that NEIL1 is able to remove the 5′-deoxyribophosphate (dRP) which results from the AP site incision [34]. Recently, NEIL1 has been reported to be involved in NER since it is able to repair (5′R)-8,5′-cyclo-2′-deoxyadenosine (R-cdA) and (5′S)-8,5′-cyclo-2′-deoxyadenosine (S-cdA), which are typical substrate for NER and not for BER. However, the mechanism by which NEIL1 acts in NER is still unknown [35].

NEIL1 interacts with several BER proteins such as POLβ, DNA ligase III (Lig III), FEN1, PCNA and XRCC1 via its C-terminal domain that is not required for *in vitro* DNA glycosylase and lyase activities [32,36,37]. While NEIL1 stimulates OGG1 cleavage, its activity is stimulated by the checkpoint protein complex Rad9-Rad1-Hus1 (9-1-1) [38] and by the Werner helicase that is defective in progeroid Werner's syndrome [39].

3.2. Relevant SNPs in this gene

The observation that *neil1* heterozygote mice present a combination of clinical manifestations known as the metabolic syndrome [6] led to investigations of human polymorphic variants of NEIL1 that possess compromised catalytic efficiencies. Two NEIL1 polymorphisms, Gly83Asp (rs5745906) and Cys136Arg (rs5745907), have been shown to be devoid of glycosylase activity. The Gly83Asp variant has been shown to be dysfunctional for 8OHG, thymine glycol, FapyA, FapyG and dihydrothymine in duplex DNA. A wild type-like glycosylase activity has been found on 5OHC and 5OHU in single stranded DNA [40]. One report indicates that the ability of the variant protein to perform δ-elimination at the abasic site is also reduced [41] although it is correctly folded. Gly83 is present in the N-terminal domain in a loop within a groove of NEIL1 in which DNA is expected to bind (Fig. 1). The active site of NEIL1 is dominated by basic amino acid side chains. Thus, the substitution of a glycine with an aspartic acid residue has been suggested to be particularly deleterious to the activity of the enzyme [41]. In the case of the Cys136Arg variant, it has been shown that the amino acid substitution alters the folding of the protein, probably compromising the ability to bind flipped nucleotides. The enzyme specificity and kinetics of other two variants, Ser82Cys (rs5745905) and Asp252Asn (rs5745926), were found very similar to wild type enzyme [41]. No association between NEIL1 variants and human disease has been reported yet.

4. NEIL2

4.1. Structure and function

Like NEIL1, NEIL2 belongs to the family of DNA glycosylases homologous to the bacterial Fpg/Nei family. The gene encoding for NEIL2 contains five exons. The NEIL2 protein structure has not been solved by crystallography yet. Two domains have been identified: the N-terminal and the C-terminal that contains the typical H2TH motif and an unusual zinc finger motif necessary for DNA binding and catalysis respectively [42,43].

NEIL2 shows the bifunctional activity, *i.e.* DNA glycosylase and AP lyase, towards oxidative products of cytosine, with the highest activity for 5OHU. A low efficiency for 5,6-dihydrouracil (DHU) and 5OHC excision has been reported, while a negligible or undetectable activity for 8OHG, thymine glycol, 2-hydroxyadenine, hypoxanthine, and xanthine has been shown. The expression profile of NEIL2 is independent of the cell cycle. Since NEIL2 shows a higher activity for excising 5OHU in bubble DNA than in duplex or single-strand DNA, its role in global genome repair has been postulated [44]. Moreover, it has been shown that oxidative stress enhances NEIL2 activity, by activating a positive responsive regulatory region within the promoter [45]. Similar to what observed for NEIL1, NEIL2 is also able to initiate an APE1-independent pathway after removal of 5OHU, which is characterized by multiple interactions of NEIL2 with downstream BER proteins, such as POLβ, Lig III and polynucleotide kinase (PNK). These findings suggest that these proteins could be recruited by NEIL2 to form a large DNA repair complex at the site of DNA damage [46]. The Y-box-binding protein-1 (YB-1) has been proposed as partner of this repair complex, since it has been shown to stably interact with NEIL2, particularly after oxidative stress [47]. NEIL2, like NEIL1, exhibits an efficient dRP-lyase activity [34].

4.2. Relevant SNPs in this gene

Two sSNPs in the 5′UTR (ss74800505 and rs8191518 SNP) have been shown to decrease NEIL2 expression level when present together, thus representing potential modifiers of disease susceptibility. The mechanistic hypothesis for this down-regulation is that these polymorphisms may compromise the binding of essential transcriptional proteins [48]. A significant increase in mutagen-sensitivity in cultured lymphocytes heterozygous or homozygous for the ss74800505 SNP has been observed, suggesting that the altered expression level of NEIL2 may affect DNA repair thus leading to increased induced mutagenesis. Another polymorphism in an intronic region of NEIL2 gene, the rs804270 SNP, has been found in association with squamous cell carcinomas of the oral cavity and oropharynx of advanced stages [49]. However, additional studies are needed to confirm this association and to characterize the phenotypic effect of this polymorphism.

5. MUTYH

5.1. Structure and function

MUTYH is a monofunctional DNA glycosylase responsible for initiating BER by excising the adenine opposite 8OHG, as well as 2-hydroxyadenine (2OHA) especially at the 2OHA:G mispair [50,51]. The resultant AP site is then cleaved by APE1 and the repair process completed by downstream BER enzymes.

The MUTYH gene comprises sixteen exons (Fig. 1). Ohtsubo et al. [51] showed that there are three classes of mRNA transcripts (α, β and γ) that are alternatively spliced producing several mature transcripts. Multiple transcription initiation sites give rise to two different proteins differing in their localization which is either mitochondrial (type 1 protein) or nuclear (type 2 protein) [51].

The MUTYH structure is composed by a catalytic domain and by a C-terminal domain connected by a linker region [52,53]. Sequence alignments indicate that both domains share significant sequence homology with the bacterial MutY, while the length and the sequence of the connecting region differ [53].

The N-terminal domain of MUTYH, containing the HhH element, followed by a (Gly/Pro)-rich loop and a catalytically essential

aspartate residue (Asp222), interacts with the strand containing the substrate adenine residue, which is then completely extruded from the DNA helix and is inserted into an extra-helical pocket. This domain includes a [4Fe–4S] cluster that is not only a structural motif but also probably involved in damage recognition as transmitter of redox signal [54]. The C-terminal domain contacts the 8OHG containing strand, thus leading to 8OHG recognition [52]. It is also involved in the interaction with other downstream BER proteins [55–57].

The MUTYH glycosylase activity is stimulated by APE1 that interacts with MUTYH and promotes its turnover, thus preventing the release of potentially cytotoxic AP sites [56]. The repair of 8OHG/A mispairs requires a cross-talk between BER and MMR and coupling to DNA replication to ensure repair [58,59]. Stimulation of MUTYH activity by the MMR recognition protein MSH2/MSH6 (MutSα) and interaction with the 9–1–1 complex via Hus1 has been reported [60,61]. Moreover, MUTYH physically interacts and colocalizes at DNA replication foci with PCNA [59].

5.2. Relevant SNPs in this gene

Two polymorphisms, Gln324His (rs3219489) and Val22Met rs3219484), have been investigated for their functional activity [62] (Fig. 1). The Gln324 substitution occurs in the linker domain in a region which is not conserved in bacteria, probably involved in protein–protein interactions [53]. Results on DNA glycosylase activity of Gln324His are contradictory [62,63] while no difference in the functional activity was found for the Val22Met [62] variant that is located in the N-terminal. The Gln324His variant has been associated with increased risk of lung [64] and colorectal [65,66] cancer.

MUTYH offers the unique possibility of comparing the functional impact of germline mutations associated with cancer and common SNPs. The estimates of disease risk associated with mono-allelic and bi-allelic MUTYH carriers have been recently refined in a large-scale meta-analysis [67]. In humans, *MUTYH* germline mutations have been associated with a recessive form of familial adenomatous polyposis and colorectal cancer predisposition (*MUTYH*-associated polyposis, MAP) [5]. Several human MUTYH variants essentially due to missense or insertion/deletion mutations have been functionally characterized [62,68–71]. Generally, variants are associated with a severe reduction of the DNA glycosylase activity and show residue substitution in the catalytic domain or in the substrate recognition region. In the Tyr165Cys (rs34612342), the most common variant, the Tyr residue (Tyr88 in bacteria) directly intercalates into the DNA duplex between 8OHG and the nucleoside 5′ to 8OHG [52]. The substitution of Tyr165 with the smaller cysteine residue has been reported to produce dramatic structural changes with a reduction in both stacking interaction and inter-residue hydrogen bonding capability. Conversely, the residue substitution associated to the common SNPs described above, *i.e.* Val22Met and Gln324His, is located far from the catalytic domain and as far as the latter is concerned in a region that is missing in prokaryotic homologs.

6. APE1

6.1. Structure and function

APE1/Ref-1 (also called APEX1 or Ref-1 and here referred to as APE1) is the major mammalian 5′AP endonuclease. The human *APE1* gene consists of five exons, the first of which is untranslated [72] (Fig. 1). The promoter is characterized by the presence of two negative calcium response elements (nCaRE)-like sequences which are recognized by the APE1 polypeptide, suggesting that *APE1* gene may be down-regulated by its own product [73]. *APE1* gene is constitutively and ubiquitously expressed in human cells [74]. APE1 is characterized by two domains: the N-terminus, which contains a bipartite nuclear localization signal (NLS) and has a redox-mediated transcriptional regulatory activity [75,76], and the C-terminus that is involved in the enzymatic activity on DNA AP sites [77].

APE1 hydrolyses the 5′phosphodiester bond of the AP site to generate a DNA intermediate that contains a single strand break with 3′OH and 5′dRp termini. Besides the AP endonuclease activity, APE1 acts also as 3′ and 5′-exonuclease, 3′diesterase and 3′phosphatase, thus being able to remove the β-unsaturated aldehyde and the 3′ terminal phosphate produced by bifunctional DNA glycosylase [36]. Therefore, APE1 is the key enzyme responsible for the incision of the AP sites and for the production of a 3′OH terminus necessary for POLβ to proceed. It has been proposed that the incision of AP site by APE1 is a rapid multistep process which efficiency can be limited by a slow step of product release [78]. The conformational changes which APE1 undergoes upon binding to the substrate have been characterized. The interaction with substrate includes insertion of protein's loops into both the major and minor grooves of the DNA, flipping of the abasic nucleotide into the hydrophobic pocket of APE1, and kinking of the DNA helix [79]. Besides its repair function, APE1 acts as a transcriptional regulatory factor, thus leading to the activation or repression of many genes that are involved in cancer promotion and progression [80,81].

Finally, a new function of APE1 in RNA metabolism has been discovered. By the first thirty-three aminoacids of its N-terminal, APE1 binds RNA and may act as a cleansing factor of abasic RNA [82,83]. The APE1 ability to bind and cleave mRNA has been recently demonstrated in relation to the control of c-Myc expression [84]. Another important role of APE1 is to contribute to the coordination of the different BER steps by interacting directly or indirectly with other BER enzymes and repair proteins belonging to other pathways. Interactions with DNA glycosylases, such as OGG1, MUTYH and 3-methyladenine DNA glycosylase, and with POLβ, XRCC1, and FEN1 have been reported [83]. Post-translational modifications of APE1, such as phosphorylation, S-nitrosation, acetylation and ubiquitination have been described but the biological significance of these modifications has not been fully clarified yet. However, they seem to be crucial in determining and controlling APE1 activities (phosphorylation) and the multiple interactions with other proteins, by influencing APE1 cellular localization and intracellular transport (S-nitrosation, ubiquitination) [85]. Alternatively, post-translational modifications, such as acetylation, can modulate the transcriptional regulatory function of APE1, as shown for the recruitment of YB-1 by acetylated APE1 with the subsequent activation of the multidrug resistance gene MDR1 [86].

6.2. Relevant SNPs in this gene

A common SNP in the APE1 gene, the Asp148 Glu (rs1130409), has been reported to affect neither the AP endonuclease nor the DNA binding activity [87]. However, this SNP was significantly associated to an increased DNA damage level, as measured by comet assay on peripheral blood lymphocytes from healthy donors [88]. The Asp148Glu SNP in combination with the XRCC1 Arg399Gln (rs25487) allele has been reported to induce cell cycle delay in human lymphocytes exposed to ionizing radiation and to markedly increase the risk of breast [89] and pancreatic cancer [90], thus leading to hypothesize that these aminoacid substitutions may compromise the interaction between APE1 and XRCC1. A large meta-analysis of case–control studies, explored the association between the Asp148Glu polymorphism and cancer risk and showed that it is associated with increased risk of cancer, especially of colorectal cancer [91]. In the case of the Gly241Arg (rs33956927) substitution, no effect on DNA binding and AP endonuclease activity was also observed [87]. A polymorphism of the 5′UTR of *APE1* gene

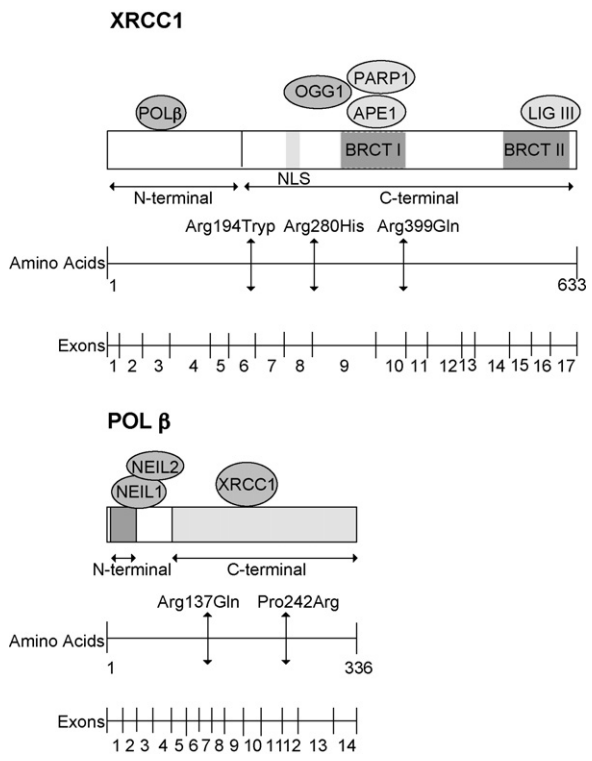

Fig. 2. XRCC1 and POLβ: protein and gene structure. The protein domains and the regions of interaction with other BER proteins are indicated. The location of the SNPs described in the text is reported.

(rs1760944), has been associated to lung cancer risk in a Chinese population [92].

7. XRCC1

7.1. Structure and function

XRCC1 is a protein devoid of any catalytic activity, which plays a crucial role in the coordination of two overlapping repair pathways, single-strand break repair (SSBR) and BER [93]. Human XRCC1 gene is composed by seventeen exons and encodes for a 70-kDa protein comprising three functional domains: the N-terminal DNA binding domain, a centrally located BRCA1 carboxy-terminal (BRCT) I and a C-terminal BRCT II domain (Fig. 2) [94]. The ability to bind DNA substrates and to interact with many DNA repair proteins suggest that XRCC1 may serve both as strand-break sensor and coordinator of DNA repair steps [95,96]. XRCC1 is involved not only in the post-incision steps, but even in the early steps of BER, as shown by its stimulatory effect on the activity of several DNA glycosylases (OGG1, 3-methyladenine-DNA glycosylase, NTH1 or NEIL2) and of APE1 [97,98]. By binding DNA substrates and by holding the proteins together through its different interacting domains, XRCC1 may help to avoid the exposure of potentially mutagenic and toxic DNA intermediates, optimizing the interaction between DNA substrates and enzymes in the BER cascade [94,95]. It has been reported that the interaction of XRCC1 with PNK, POLβ and Lig III leads to the formation of multiprotein complexes in human cell extracts [99,100]. XRCC1 is recruited to sites of oxidative and methylated DNA damage by the activated PARP-1, which interacts with the BRCT I domain of XRCC1, leading to the formation of repair foci [101,102]. The assembly and activity of SSBR protein complexes at sites of chromosome breakage require the phosphorylation of XRCC1, mediated by the casein kinase II (CK2) [100].

7.2. Relevant SNPs in this gene

XRCC1 is highly polymorphic and the most frequent and widely studied SNPs are Arg194Trp (rs1799782), Arg280His (rs25489), and Arg399Gln (rs25487). Functional assays in cells in culture have shown that the expression of the XRCC1 194Trp allele in XRCC1 defective cells fully restored DNA repair after alkylation damage, as the wild-type allele [103]. Accordingly, a recent study has shown that this SNP stabilizes XRCC1 activity. The mechanism involves the activation of the translation of the variant protein as a consequence of the stronger binding affinity of a micro-RNA (miRNA), mir-138, for the variant allele [104]. These findings give a plausible biological explanation for the association of XRCC1 194Trp variant with decreased cancer risk as inferred from a meta-analysis of 38 case–control studies addressing different types of cancer [105]. However, an increased risk of lung cancer has been reported in individuals homozygous for this variant [106].

In contrast, the XRCC1 280His allele seems to have a deleterious functional impact on XRCC1 activity as shown by only partial restoration of DNA repair capacity of XRCC1 defective cells in complementation assays [103]. This variant has been associated to an increased risk of bladder cancer [107].

The Arg399Gln SNP occurs in the BCRT I domain and might thus affect the interaction of XRCC1 with APE1 and PARP1 (Fig. 2). Contrasting results have been obtained for the phenotypic effect of this variant. Cells defective in XRCC1 showed reduced SSBs after alkylation damage [88] and increased micronuclei frequency after bleomycin treatment [108], when complemented with this variant. Moreover, both decreased [109] and increased *in vitro* repair [110] efficiency has been reported for peripheral blood lymphocytes from individuals homozygous for the XRCC1 399Gln variant, following γ-irradiation. Meta-analysis studies showed that individuals homozygous for Arg399Gln are at increased breast cancer risk in the Asian but not in the Caucasian population [111]. This variant was also found to be associated to head and neck cancer in Caucasians even if with a marginal statistical significance and similar results were obtained for the Arg194Trp SNP [112]. Recently, an increased risk of childhood acute lymphoblastic leukemia was observed in association with XRCC1 heterozygous and homozygous Arg399Gln genotypes [113]. The homozygous genotype was also associated with increased risk for coronary atherosclerosis [114]. No association was found between the polymorphisms in XRCC1 (Arg399Gln, Arg280His and Arg194Trp) and risk of colorectal cancer in two recent meta-analyses [115,116].

A SNP in the XRCC1 promoter region (−77T > C, rs3213245) which could alter the binding affinity of the transcription factor Sp1 has been described [117–119]. This polymorphism when present together with SNPs in other BER genes was associated with increased bladder cancer risk [107].

8. POLβ

8.1. Structure and function

POLβ is a 39 kDa monomeric protein which belongs to the X-family of polymerases. Human POLβ is encoded by a 34 kb single-copy gene, composed of fourteen exons which can be alternatively spliced to give rise to several transcripts [120,121]. POLβ is folded into two distinct domains, each associated with a specific functional activity: the amino-terminal (8 kDa) and the carboxy-terminal (31 kDa) domain that are connected by a protease sensitive hinge region (Fig. 2). The 8 kDa N-terminal domain mediates the lyase activity of POLβ which removes the 5′dRp terminus produced by the AP endonuclease activity of APE1. Moreover, this domain carries a single-stranded DNA binding activity

necessary to direct POLβ to short gaps possessing a 5′-phosphate termini [122]. Finally, the 8 kDa domain is responsible for the processivity of the POLβ-mediated DNA synthesis, when a gap spanning from 1 to 6 nucleotides is present [123]. The 31 kDa C-terminal domain accounts for the polymerase activity and is composed of three subdomains: the catalytic, the duplex DNA binding and the nascent base pair binding subdomain [124]. POLβ is involved in both sub-pathways of BER, the short-patch (SP-BER) and the long-patch BER (LP-BER) [125]. In the SP-BER, POLβ catalyzes the insertion of one nucleotide to the 3′-end of the nicked AP site, and then excises the 5′dRP residue, leaving a nick that can then be sealed by the XRCC1/Ligase IIIα complex [126]. In LP-BER, POLβ or the alternative replicative polymerases (Pol δ/ε) perform strand displacement synthesis, generating a DNA flap of 2–10 nucleotides, which is removed by flap endonuclease 1 (FEN1) [125]. POLβ has been reported to interact with many proteins, such as XRCC1 [127], proliferating cell nuclear antigen (PCNA) [128], and FEN1 [129]. These interactions promote the recruitment of proteins to the DNA repair site, the stimulation of enzyme activities and the coordination of the BER enzymatic cascade.

8.2. Relevant SNPs in this gene

Two single nucleotide substitutions that lead to amino acid changes, Arg137Gln (rs12678588) and Pro242Arg (rs3136797), have been identified as nsSNPs in human *pol*β gene but only the Arg137Gln has been extensively characterized. This variant is characterized by a reduced polymerase activity and an impaired interaction with PCNA; moreover, it affects BER efficiency when tested in reconstitution assay, thus leading to hypothesize that it contributes to genomic instability and cancer development [130]. The Arg137 forms hydrogen bonds with other adjacent amino acid residuals in the catalytic domain [131]. Its substitution with a glutamine residue might disrupt the formation of these bonds, thus impairing the polymerase activity [130]. Moreover, Arg137 is a site of methylation. This post-translational modification has been shown to block the interaction between POLβ and PCNA, thus being a regulatory mechanism of the BER pathway [132]. This mode of BER regulation is lost in cells carrying the Arg137Gln polymorphism, since POLβ cannot be methylated [130]. The expression of the Arg137Gln POLβ variant in *pol*β null mouse embryonic fibroblasts failed to restore cellular resistance to alkylating agents [130]. A polymorphism of a splicing acceptor site (rs33918599), namely the exon 14 acceptor site, has been discovered. It is predicted to improve the acceptor site, but its functional consequences are still unknown [121]. Many other polymorphisms have been found in *pol*β gene, none of which has been individually related to risk of disease. On the contrary, the haplotype analysis has shown that the combination of four intronic SNPs (rs2272615, rs2953983, rs3136717, rs3136795) was associated with an increased bladder cancer risk [133].

9. PARP1

9.1. Structure and function

PARP1 is a multifunctional enzyme which plays a key regulatory role in BER [36] and in many other cellular processes, such as replication [134], telomere maintenance [135], transcription and chromatin remodeling [136]. In response to SSB formation either as DNA repair intermediates or by direct attack of genotoxic agents, PARP1 uses nicotinamide-adenine dinucleotide (NAD) as substrate to catalyze the covalent transfer of ADP-ribose (ADPr) to nuclear protein acceptors or to an existing polyADPr chain [137]. This post-translational modification induces an increase in negative charge in the target proteins, which then lose DNA-binding affinity [138].

PARP1 gene contains twenty-three exons which code for a 113 kDa nuclear protein [139]. PARP1 protein structure encompasses three main domains, which have been functionally characterized and more recently subdivided in smaller domains (A-F) [140]. The N-terminal DNA region which comprises two zinc-fingers motifs (domain A) is responsible for DNA lesion recognition and chromatin condensation; the domain B contains the NLS; the automodification domain includes a BRCT repeat motif which can be modified by ADPr and is required for dimerization, and the C-terminal catalytic domain is responsible for ADPr transfer [141,142]. Recently, a third zinc domain has been described in human PARP1 and suggested to allow communication between the N-terminal and the C-terminal through conformational changes [143].

In BER, PARP1 plays a regulatory role, by blocking the access of repair enzymes to the site of DNA damage [144], through its binding with the repair intermediates. It seems that, by attaching a pADPr chain to itself through glutamate/aspartate [145], and/or lysine residues [146], PARP1 dissociates from DNA breaks, allowing BER to proceed [144]. In particular, PARP1 seems to be involved in LP-BER, by playing an inhibitory effect on the POLβ-dependent DNA synthesis [147] and protects excessive SSBs from conversion into lethal DNA double strand breaks (DSBs) [148]. Finally, it has been demonstrated that PARP1 is able to physically interact with XRCC1, POLβ and Lig III, without affecting the SP-BER efficiency, thus leading to the hypothesis that it acts as SP-BER coordinator [101,149].

9.2. Relevant SNPs in this gene

Several SNPs have been found in *PARP1* gene [150], but only for the Val762Ala (rs1136410) a functional analysis has been performed. This amino acid substitution is responsible for a reduced activity of PARP1, thus being potentially correlated to an increased risk of disease [151]. Three studies have reported positive associations between the Val762 SNP and lung [152], esophagous [117], and prostate cancer [153]. The interaction between the Val762Ala and the intronic polymorphism of POLβ (rs3136717) resulted in increased bladder cancer risk [150]. Two of four haplotypes (rs1805404 and rs1136410), which derive from amino acid substitutions at position 81 and 762, have been significantly associated with an increased risk of Alzheimer's disease [154].

10. Assays for genotype-phenotype correlations

As shown above the information on the functional consequences of SNPs in oxidative DNA damage repair genes is very limited. Today, due to the effort in whole genome sequencing, we have identified an even larger number of nsSNPs but the challenge remains the development of functional assays. The knowledge of protein structure–function relationship can aid in the prediction of whether a SNP will alter protein function and cause disease but the biological assay remain the ultimate validation of its contribution to the risk of disease development. Two types of assays are currently available to address genotype-phenotype correlations: cell-free assays that interrogate cell extracts for specific enzymatic functions and cell-based assays that usually rely on recombinant DNA technology to express the polymorphic genes in cells or, in some cases, in animals.

The enzymatic assay for the activity of 8OHG DNA glycosylase in protein extracts prepared from human blood cells developed by Paz-Elizur et al. [155] is an example of an epidemiology-grade

in vitro functional assay. This assay monitors the ability of protein extracts from peripheral blood mononuclear cells (PBMC) to remove an 8OHG residue (OGG activity) from a radiolabeled synthetic duplex oligonucleotide containing a single site-specific 8OHG. OGG1 is the major enzyme responsible of this reaction but other DNA glycosylases could contribute too. Moreover, inter-individual variations in other repair proteins (*e.g.* APE1 and NEIL1), may affect the efficiency of this reaction underscoring the advantage of using an activity assay, which integrates also stimulators and activators. Following removal of the oxidized base the resultant abasic site is cleaved, generating a shorter radiolabeled DNA product that can be distinguished on the basis of its size by urea-polyacrylamide gel electrophoresis. The quantification of the substrate oligonucleotide and the cleaved product allows the evaluation of the cleavage activity of 8OHG in the extracts under test. We have applied a slightly modified version of this assay that is based on the use of a fluorescently labeled DNA substrate [156] to monitor the ability of PBMC from normal subjects to remove 8OHG with the aim of correlating activity with genotype. We have confirmed that the homozygous OGG1 Ser326Cys genotype is associated with reduced cleavage activity but not with reduced gene expression (unpublished data). When functional assays in blood cells are used as surrogate for the measurement of the activity in the cancer target organ the question arises of whether the activity in blood linearly correlates to the activity in the target organ. In a study conducted on PBMC from patients with non-small cell lung cancer and lung cancer [157] the reduced OGG activity was shown to linearly correlate to OGG activity in the non-tumor lung tissue in non-small cell lung cancer. This approach should be taken when possible for any functional assay performed in blood cells.

The cell-based assays require cells that are completely lacking the gene whose polymorphic sequences have to be tested for function, and a biological assay able to distinguish deleterious versus neutral variants. In the case of genes involved in DNA damage response either sensitivity to DNA damaging agents (challenge assay) or DNA repair capacity (DRC) can be used as end-points. This approach to phenotyping has been recently extensively reviewed [158] and therefore it will be briefly mentioned here. The challenge assay consists in the analysis of chromosome breakage after challenging cells *in vitro* with DNA damaging agents [159]. The challenge assay has been validated to indicate abnormal DNA repair responses to a variety of DNA damaging agents on the basis of studies using the host cell reactivation assay and patients with specific DNA repair defects. The DRC can be measured by using either the comet assay or the host cell reactivation assay. The comet assay evaluates the repair capacity of a cell that has been damaged experimentally by using single cell gel electrophoresis [160]. Modifications of this technique allow addressing specific types of damage (and therefore the functionality of specific DNA repair variants) by using enzymes that convert into SSBs the lesions of interest (*e.g.* formamidopyrimidine DNA glycosylase (fpg)-sensitive sites) [161]. The host cell reactivation assay measures cellular DRC by using an exogenous plasmid DNA as substrate [162]. The plasmid can be damaged with different agents thus allowing testing the functionality of different DNA repair pathways. To interrogate the DSB repair capacity of a cell a widely used assay is the phosphorylation of the histone γ-H2AX by DNA damage-activated kinases [163]. However, the specificity of this assay for DSBs is a matter of debate. Finally, gene expression profiling of DNA repair genes can provide information on the different DNA repair pathways [164] but an important drawback of this approach is that post-translational modifications of DNA repair enzymes that are known to affect organelle targeting and repair activity are not taken into account. All these assays allow testing the functionality of a protein within the cell environment where the complex network of interactions and regulatory mechanisms is active, thus conferring a clear advantage to these assays as compared to the *in vitro* tests. We have provided above examples of these assays used to test the functionality of BER variants by either expressing the mutant proteins within defective cells or by using cells with the genotype of interest and then testing survival or DRC after exposure to DNA-damaging agents.

Of interest is a recently developed functional assay designed to test for SNPs found in the BRCA2 gene. Mutations in this gene have been associated with the hereditary development of breast and ovarian cancer. More than 800 mutations have been reported from sequencing of BRCA2 gene of patients with a family history of breast cancer but the lack of information on their function leave patients with an ambiguous answer as to their cancer risk. Kuznetsov et al. [165] developed an assay to test for the functional significance of BRCA2 mutations using mouse embryonic stem cells (ES). This assay is based on the finding that ES cells completely lacking BRCA2 are not viable and therefore only cells with an introduced (via bacterial artificial chromosomes) BRCA2 sequence capable of supporting viability survive. These cells once established can be evaluated in additional assays to assess BRCA2 functions. This technique may also serve as a paradigm for functional analysis of mutations in other genes linked to human diseases.

11. Conclusions

SNPs represent the most common mutations in humans by accounting for about 90% of sequence polymorphisms in humans; however, as reviewed here for oxidative DNA repair genes, for most of them the functional consequences are unknown and only for a few of them there is some evidence of association with increased risk of disease. So, at a first glance, this finding suggests that their functional consequences are milder than those due to known disease-causing mutations (either inherited or acquired) and that probably common SNPs should be present in more than one critical gene to trigger disease onset. In the presence of multiple susceptibility alleles an analysis based on haplotypes can be advantageous over an analysis based on individual SNPs, particularly when linkage disequilibrium between SNPs is weak [166]. It remains that it is of great importance to identify those SNPs with functional consequences because they could contribute to or cause pathology onset. The currently available biological assays are far from being automated and require technical skills. Even though the ultimate validation remains a biological assay that directly measures the consequence of the mutation in question, various computational, predictive methods have been exploited to prioritize the large number of SNPs identified on the basis of their functional consequences. Several lines of evidence suggest that the distribution of the residue changes in the protein structure might be a relevant factor to determine the functional activity of the protein. In this respect, a systematic study has been performed with protein kinases, taking into account the location of sSNP and nsSNPs among other mutations, with respect to the evolutionary storage of the primary sequence, the structurally important regions and the functional regions [167–169]. This analysis has identified specific regions of the catalytic core that are most sensitive to change and has shown that mutations involving amino acids with specific structural functions in proteins are more likely to cause disease. Accordingly, none of the nsSNPs of BER repair genes reviewed here was found in association with a complete loss of enzyme activity, neither substitutions were localized in catalytic core regions. Only for a few common SNPs, such as the Ser326Cys variant of OGG1, the Val762Ala of PARP1 and the Arg280His of XRCC1, both a slight functional reduction and an association with increased risk of disease were reported (Table 1). By analyzing the structure-function relationship, in the case of OGG1 and NEIL1, the SNPs are

Table 1
Functional significance, association with disease and frequency of common SNPs in oxidative DNA damage repair genes.

Gene	SNP	Functional activity (*in vitro*/*in vivo*)	Association with disease	Allelic frequency in global population*
OGG1	Ser326Cys (rs1052133)	Low catalytic activity Increased micronuclei Reduced cell 8OHG repair	Lung and bladder cancer Huntington's disease	C 0.675; G 0.325
NEIL1	Gly83Asp (rs5745906)	Defective catalytic activity	–	A 0.006; G 0.994
	Cys136Arg (rs5745907)	Altered protein folding Lack of DNA glycosylase activity	–	A 0.006; G 0.994
	Ser82Cys (rs5745905)	Normal catalytic activity	–	C 0.994; G 0.006
	Asp252Asn (rs5745926)	Normal catalytic activity	–	G 0,988; A 0,012
NEIL2	5′UTR (ss74800505)	Decreased gene expression Increased mutagen-sensitivity	–	G 0.986; T 0.014
	5′UTR (rs8191518)	Decreased gene expression	–	C 0.903; G 0.097
	Intronic region (rs804270)	–	Squamous cell carcinomas of oral cavity and oropharynx	C 0.572; G 0.428
MUTYH	Gln324His (rs3219489)	–	Lung and colorectal cancer	C 0.406; G 0.594
	Val22Met (rs3219484)	Normal catalytic activity	–	A 0.017; G 0.983
	Tyr165Cys	Significantly decreased catalytic activity	–	
APE1	Asp148Glu (rs1130409)	Normal AP endonuclease Normal DNA binding Cell cycle delay after DNA damage Increased DNA breaks	Breast, pancreatic and Colorectal cancer	G 0.465; T 0.535
	Gly241Arg (rs33956927)	Normal catalytic activity	–	–
	5′UTR (rs1760944)	–	Lung cancer	G 0.570; T 0.430
XRCC1	Arg194Trp (rs1799782)	Normal DNA repair Increased gene expression	Decreased cancer risk Lung and head and neck cancer	C 0.881; T 0.119
	Arg280His (rs25489)	Defective DNA repair	Bladder cancer	G 0.897; A 0.103
	Arg399Gln (rs25487)	Defective DNA repair and increased micronuclei	Breast and head and neck cancer Childhood acute lymphoblastic leukemia Coronary atherosclerosis	A 0.232; G 0.768
	Promoter (rs3213245)	–	Bladder cancer	C 0.224; T 0.776
POL β	Arg137Gln (rs12678588)	Reduced DNA polymerase activity Impaired interaction with PCNA Decreased BER efficiency Increased sensitivity to DNA damage	–	–
	Intronic (rs33918599)	Improved acceptor site	–	–
	Intronic (rs2272615)	–	Bladder cancer	G 0.241; A 0.759
	Intronic (rs2953983)	–	Bladder cancer	T 0.258; C 0.742
	Intronic (rs3136717)	–	Bladder cancer	C 0.236; T 0.764
	Intronic (rs3136795)	–	Bladder cancer	G 0.965; A 0.035
PARP1	Val762Ala (rs1136410)	Reduced activity	Lung, esophagous, prostate and bladder cancer	T 0.812; C 0.188
	Intronic (rs1805404) (A/G/C/T)	–	Alzheimer's disease	C 0.795; T 0.205

* The NIH Polymorphism Discovery Resource (NIHPDR) 90 individual screening subset has been taken as reference.

localized in the neighboring of the active site domain, while in the case of MUTYH, APE1, XRCC1 and POLβ they are present in regions involved in the interaction with other proteins. There are also a few examples of SNPs located in sites important for post-translational modifications with a regulatory role (*e.g.* Arg137Gln variant of POLβ). In all cases a slight if any functional effect is recorded. In contrast, cancer-associated germ-line mutations of MUTYH are mostly located in the catalytic domain and/or highly conserved regions of the protein and lead to severe reduction of the enzymatic activity.

Finally, a topic for future research is the relevance of SNPs in non-coding regions for human disease. Many non-coding regions are transcribed and may affect cell functions and even changes in wobble bases that do not affect amino acid sequence may affect the rate of translation. miRNAs are important regulators of eukaryotic gene expression [170] and SNPs in DNA repair proteins may affect this regulatory pathway. An example is provided by the Arg194Trp variant of XRCC1 that increases the binding affinity of a miRNA leading to an increase in protein levels [104]. Moreover, SNPs within miRNA target sites have been claimed to be associated with a variety of human diseases. A positive association has been reported between miRNA-binding sites SNPs and risk of sporadic colorectal cancer [171]. Future studies should address the relevance of genetic alterations in these critical sites.

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