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Base excision repair: A critical player in many games

Susan S. Wallace*

Department of Microbiology and Molecular Genetics, The Markey Center for Molecular Genetics, The University of Vermont, 95 Carrigan Drive, Stafford Hall, Burlington, VT 05405-0084, USA

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ABSTRACT

This perspective reviews the many dimensions of base excision repair from a 10,000 foot vantage point and provides one person's view on where the field is headed. Enzyme function is considered under the lens of X-ray diffraction and single molecule studies. Base excision repair in chromatin and telomeres, regulation of expression and the role of posttranslational modifications are also discussed in the context of enzyme activities, cellular localization and interacting partners. The specialized roles that base excision repair play in transcriptional activation by active demethylation and targeted oxidation as well as how base excision repair functions in the immune processes of somatic hypermutation and class switch recombination and its possible involvement in retroviral infection are also discussed. Finally the complexities of oxidative damage and its repair and its link to neurodegenerative disorders, as well as the role of base excision repair as a tumor suppressor are examined in the context of damage, repair and aging. By outlining the many base excision repair-related mysteries that have yet to be unraveled, hopefully this perspective will stimulate further interest in the field.

1. Base excision repair overview

Base excision repair (BER) is a highly conserved pathway from bacteria to humans and is responsible for repairing the vast majority of endogenous DNA damage including alkylations, oxidations, deaminations and depurinations, as well as single-strand breaks (SSBs) (for reviews see [1,2]. Thus, the primary function of BER is to remove these frequently produced lesions and maintain genomic integrity. However, as discussed below, the enzymes involved in BER have been co-opted to take part in a variety of apparently unrelated cellular functions (see Fig. 1). Although BER will be discussed in general terms, this perspective will focus on the first two steps of the process in mammals, where the enzymes involved are homologous across species. Since this article covers such a broad range of topics, recent reviews will be the primary material referenced with apologies to the investigators who originally reported the observations.

The initial step in BER is the search for the lesions in DNA by DNA glycosylases. In humans there are eleven of these enzymes, four devoted to the removal of mispaired uracil and thymine, six to the repair of oxidative damage, and one to the removal of alkylated bases. The glycosylases that recognize uracil, thymine, and alkylated bases are monofunctional, and remove the damaged base by cleaving the *N*-glycosyl bond between the base and the sugar. The resulting abasic site is recognized by an apurinic (AP) endonuclease (APE1), which cleaves the abasic site leaving a sugar attached to the 5′ side of the nick. The resulting 3′ hydroxyl is a substrate for the repair polymerase, DNA polymerase β (Pol β), which also has a lyase activity that removes the sugar attached to the 5′ phosphate. The gap is filled in and sealed by a DNA ligase. The glycosylases that recognize oxidative lesions are bifunctional and not only excise the damaged base but also cleave the DNA backbone, leaving either an α, β unsaturated aldehyde or a phosphate attached to the 3′ side of the nick. The sugar is removed by the phosphodiesterase activity of APE1 and the phosphate group by polynucleotide kinase (PNK). The remainder of the steps are the same as described for the pathway initiated by the monofunctional enzymes. This process is called short patch BER and in some circumstances can be redirected to a longer patch process, often because the sugar is inefficiently removed from the 5′ end of the nick. In this case a number of different polymerases can take over, including the replicative polymerases or pol λ. The damage-containing strand is displaced and removed by FEN1, and the nick is sealed by a ligase. Ligase 1 seals

* Tel.: +1 802 656 2164; fax: +1 802 656 8749.
E-mail address: Susan.Wallace@uvm.edu

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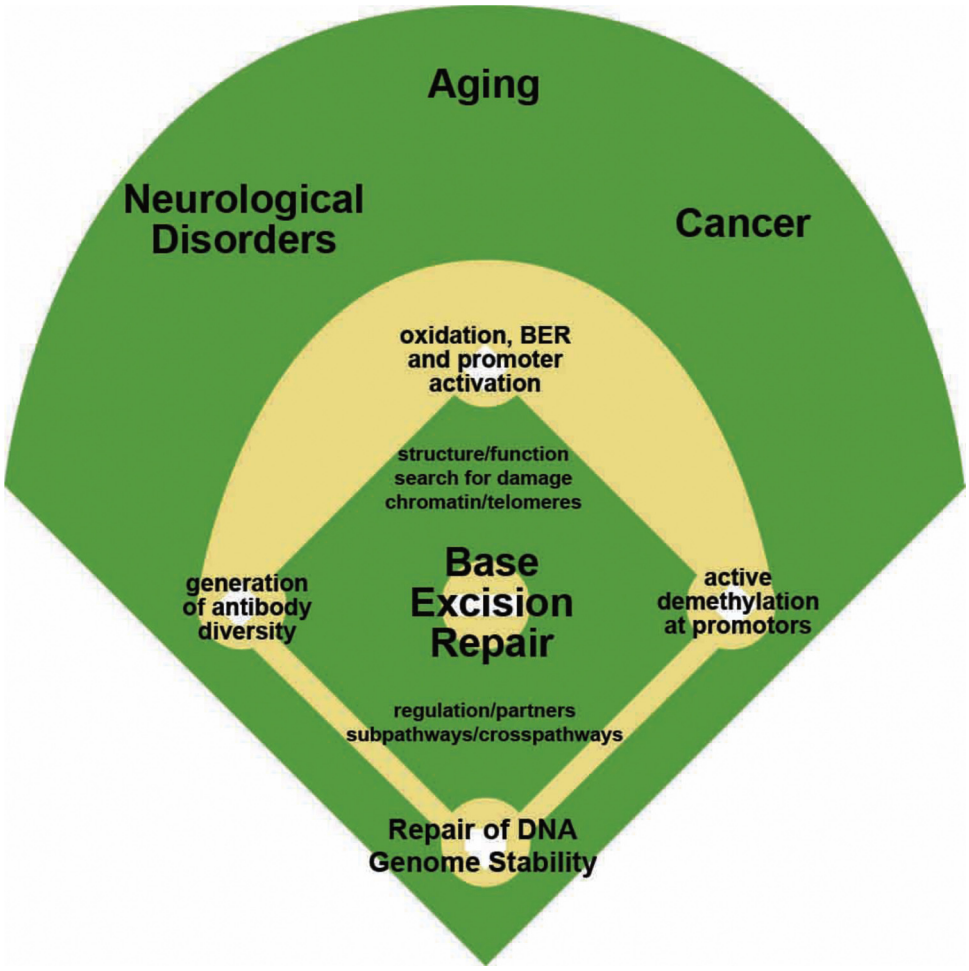

Fig. 1. This cartoon was inspired by the 1996 Failla lecture delivered by the Author to the Radiation Research Society discussing base excision repair of radiation-induced free radical damage. The model of the baseball diamond based on Abbot and Costello's skit "Who's on First, What's on Second, I Don't Know's on Third," was used to describe the activities of the four sets of BER enzymes, the glycosylases (first base), AP endonucleases (second base), DNA polymerases (third base), and ligases (home plate), which was about the extent of what was known at the time. This cartoon jumps almost two decades to display in outline form our current knowledge of BER processing which has definitely come from the minor to the major leagues.

the nick in long patch BER and either ligase 1 or ligase IIIα/XRCC1 seals the nick in short patch BER. If the starting lesion is an abasic site, repair is initiated by APE1 but the subsequent enzymatic steps are the same. Single-strand breaks may have any one of a number of end blocks that need to be removed (see Section 6) before repair can proceed. Poly(ADP)ribose polymerase 1 (PARP1), and XRCC1, a scaffolding protein, are also important players in the BER process.

The mammalian DNA glycosylases that recognize base damages all have structural or functional homologs in bacteria and in fact the human enzymes are able to complement repair defects in bacteria (for reviews see [3,4]). The human monofunctional glycosylases recognize a broad spectrum of lesions. Alkyl guanine glycosylase/methyl purine glycosylase (AGG/MPG) recognizes alkylated purines and ethenopurines and is primarily found in mammals. Uracil DNA glycosylase (UNG) removes uracil as well as 5-hydroxyuracil and other uracil derivatives in both single- and double-stranded DNA. Single-strand-selective monofunctional uracil glycosylase 1 (SMUG1) recognizes many of the same substrates as UNG in single- and double-stranded DNA including 5-hydroxymethyluracil (5-hmU). Thymine DNA glycosylase (TDG) removes uracil, thymine and 5-hydroxymethyluracil when paired with guanine in double-stranded DNA. Methyl CpG binding domain protein 4 (MBD4) recognizes uracil, thymine and 5-hydroxymethyluracil when paired with guanines in CpG dinucleotides as well as other substrates recognized by the uracil glycosylases. MUTYH, also a monofunctional glycosylase, removes adenine when misincorporated opposite 7,8-dihydro-8-oxoguanine (8-oxoG) or 2,6-diamino-4-hydroxy-5-formamidopyrimidine (FapyG).

Both OGG1 and NTH1 are bifunctional housekeeping glycosylases. In double- stranded DNA, the principal substrates for OGG1 are 8-oxoG and FapyG paired with cytosine while those for NTH1 are oxidized pyrimidines and formamidopyrimidines. The bifunctional Nei-like proteins NEIL1 and NEIL2 remove oxidized pyrimidines and formamidopyrimidines in both single-stranded and duplex DNA, although NEIL2 prefers single-stranded DNA. NEIL3 also recognizes a broad spectrum of oxidized pyrimidines and formamidopyrimidines but has weak glycosylase activity on duplex DNA and weak lyase activity on all substrates [5]. The best substrates for all of the NEIL proteins are the further oxidation products of 8-oxoG, spiroiminodihydantoin (Sp) and guanidinohydantoin (Gh) (for a review see [6]).

APE1, which has $3 \rightarrow 5$ exonuclease and $3'$ phosphodiesterase activities in addition to its AP endonuclease activity, is also highly conserved from *Escherichia coli* to humans (for a review see [7]) The N-terminal domain of APE1 contains a redox regulatory region. A second APE family member, APE2, has only weak AP endonuclease activity but strong $3'$ phosphodiesterase and $3' \rightarrow 5'$ exonuclease activities. Different DNA polymerases and DNA ligases are used across phyla for repair synthesis and

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