available at www.sciencedirect.com

ScienceDirect

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

The mechanics of base excision repair, and its relationship to aging and disease

*David M. Wilson III, Vilhelm A. Bohr**

Laboratory of Molecular Gerontology, National Institute on Aging, Baltimore, MD 21224, United States

ARTICLE INFO

Article history:
Published on line 16 November 2006

Keywords:
DNA damage
Base excision repair
Aging
Cancer
Neurodegeneration

ABSTRACT

Base excision repair (BER) is the major pathway responsible for averting the mutagenic and cytotoxic effects of spontaneous hydrolytic, oxidative, and non-enzymatic alkylation DNA damage. In particular, this pathway recognizes and repairs base modifications, such as uracil and 8-hydroxyguanine, as well as abasic sites and DNA single-strand breaks. In this review, we outline the basic mechanics of the BER process, and describe the potential association of this pathway with aging and age-related disease, namely cancer and neurodegeneration.

1. Overview

DNA is subject to spontaneous hydrolytic decay, to attack by reactive oxygen species (ROS) generated during normal cellular respiration or from exposure to certain environmental agents, and to modification by both endogenous and exogenous alkylating compounds [1]. Associated DNA damage/intermediates include, but are not limited to, uracil, 8-hydroxyguanine (8-OH-dG), 3-methyladenine, apurinic/apyrimidinic (AP) sites, and single-strand breaks (SSBs). These lesions present mutagenic and/or cytotoxic (blocking) challenges to the cell if encountered during chromosome replication or gene transcription. In Fig. 1, we have illustrated the relationship between the mutagenic potential and the frequency of occurrence for a few important lesions. When considering biological relevance, both of these parameters, as well as others need to be taken into account.

To avert the deleterious consequences of DNA damage, organisms have evolved DNA repair mechanisms, such as base excision repair (BER), to recognize, excise, and accurately replace specific forms of genetic modifications [2,3]. BER is acknowledged as the "workhorse" pathway, responsible for correcting most common forms of DNA damage. The BER process consists of the following steps: (i) excision of an inappropriate base moiety (e.g. 8-OH-dG), (ii) incision at the resulting abasic site, (iii) replacement of the excised nucleotide, (iv) clean-up of the terminal end(s), and (v) sealing of the final nick (Fig. 2). While each step in principle can be performed in isolation (i.e. independently), biochemical and structural biology studies support a model whereby the proteins of BER act in a concerted, cooperative manner to carry out the repair response, termed "passing the baton" [4]. In addition, while the BER process can be reconstituted in vitro with only a few proteins (as few as four), it has become apparent that several "auxiliary" protein components can influence the accuracy, efficacy, and molecular outcome of the BER event. In this review, we highlight some of the key mechanistic details of the BER pathway, and describe aspects of the relationship of this pathway to human disease and the aging process. Our focus is primarily on nuclear BER, but a brief discussion of mitochondrial (mt) BER is provided at the end.

2. Basic mechanics of the BER process

The first step of BER typically involves the recognition and excision of an inappropriate base (Fig. 2, left). Such substrate

* Corresponding author. Tel.: +1 410 558 8223; fax: +1 410 558 8157.
E-mail address: BohrV@grc.nia.nih.gov (V.A. Bohr).
1568-7864/$ – see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.dnarep.2006.10.017

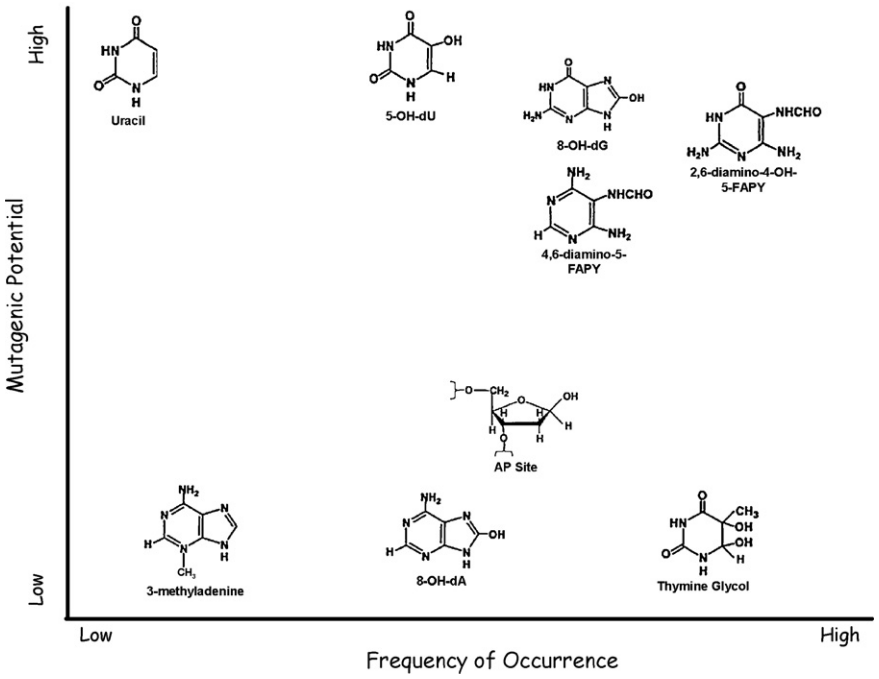

Fig. 1 – Frequency of occurrence and mutagenic potential of certain base and sugar damages. Note low to high orientation of graph. Chemical composition of the damage is shown, and name/type of lesion is indicated below. Frequency of occurrence is related to spontaneous hydrolysis (AP site), deamination (uracil), oxidation, or non-enzymatic alkylation. Mutagenic potential refers to the efficiency of bypass and the likelihood of inaccurate duplication by the replication machinery, i.e. proofreading DNA polymerases. In general, error-prone (exonuclease-deficient) polymerases are more capable of lesion bypass and mis-incorporation. As a rule of thumb, the lower the mutagenic potential, the greater the blocking potential, with 8-OH-dA serving as a noticeable exception.

bases include, but are not limited to, uracil, 3-methyladenine, 8-OH-dG, and formamidopyrimidines (Fig. 1). To execute this initial step of BER, organisms are equipped with enzymes termed DNA glycosylases [5–7]. Such proteins specifically recognize a defined set of base modifications and catalyze hydrolysis of the *N*-glycosylic bond. The resulting product is an abasic site with an intact DNA phosphodiester backbone. Monofunctional glycosylases, i.e. proteins that exhibit only glycosylase activity, often remain bound to the DNA product, purportedly protecting the abasic site from spontaneous strand cleavage and/or serving as a beacon for subsequent repair events (see below). Furthermore, some glycosylases, such as 8-oxoguanine glycosylase (OGG1) and the endonuclease VIII-like protein (NEIL1), are bifunctional [8,9]. That is, these enzymes not only excise the substrate base, but incise the DNA backbone immediately 3′ to the AP site product via a β- or β,δ-elimination reaction. The resulting single-strand break, which harbors a 3′-α,β-unsaturated aldehyde or a 3′-phosphate, respectively, requires "clean-up" and conversion to a normal 3′-hydroxyl group prior to polymerization and/or ligation.

After either removal of the substrate base or incision 3′ to the abasic site by a bifunctional DNA glycosylase, the predominant protein responsible for executing the next step of mammalian BER is apurinic endonuclease 1, APE1 [10,11]. APE1 harbors the ability both to incise immediately 5′ to an AP site (Fig. 2, left) and to remove 3′-obstructive termini, particularly 3′-α,β-unsaturated aldehyde residues (Fig. 2, right). In situations involving 3′-phosphate termini, the enzyme polynucleotide kinase/phosphatase (PNKP) is primarily responsible for excising such blocking groups in vivo [12,13] (Fig. 2, right). Nonetheless, APE1 likely serves as a back-up in this capacity, as this enzyme likewise exhibits an, albeit poor, 3′-DNA phosphatase activity [14].

Some have proposed that AP site-bound DNA glycosylases facilitate the BER response, specifically APE1 recognition and processing. However, there are no reported instances where a DNA glycosylase stimulates APE1 AP site incision activity. Instead, studies have found that APE1 promotes glycosylase activity by displacing a product-bound DNA glycosylase and relieving AP site inhibition, resulting in increased glycosylase turnover [15–23].

The combination of biochemical and structural studies supports cooperation between APE1 and the next enzyme in the BER pathway, DNA polymerase β [24,25]. POLβ both replaces the excised damaged nucleotide and removes the 5′-terminal abasic fragment left behind by APE1 incision [26] (Fig. 2). In vitro analysis has demonstrated that APE1 promotes the removal of 5′-deoxyribose phosphate groups by POLβ AP lyase activity [24]. More recent X-ray crystallography studies, coupled with basic structure-function analysis of APE1, validate the "passing the baton" model, where APE1 hands off its incised product to the next enzyme in the repair process, POLβ [25]. Work aimed at delineating the precise mechanics of this coordinated response, and demonstrating the significance of this biochemical phenomenon with respect to the cellular repair of AP sites is a major future objective.