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ScienceDirect
Mutation Research 614 (2007) 56–68
Fundamental and Molecular Mechanisms of Mutagenesis
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Organ and cell specificity of base excision repair mutants in mice

Elisabeth Larsen [a,*], Trine J. Meza [a], Liv Kleppa [a], Arne Klungland [a,b]

[a] *Centre for Molecular Biology and Neuroscience and Institute of Medical Microbiology, Rikshospitalet-Radiumhospitalet HF, 0027 Oslo, Norway*
[b] *Department of Nutrition, Institute of Basic Medical Science, University of Oslo, Postbox 1046, Blindern N-0316, Oslo, Norway*

Received 14 October 2005; received in revised form 17 January 2006; accepted 21 January 2006
Available online 12 June 2006

Abstract

Genetically modified mouse models are a powerful approach to study the relation of a single gene-deletion to processes such as mutagenesis and carcinogenesis. The generation of base excision repair (BER) deficient mouse models has resulted in a re-examination of the cellular defence mechanisms that exist to counteract DNA base damage. This review discusses novel insights into the relation between specific gene-deletions and the organ and cell specificity of visible and molecular phenotypes, including accumulation of base lesions in genomic DNA and carcinogenesis. Although promising models exist, there is still a need for new models. These models should comprise combined deficiencies of DNA glycosylases which initiate the BER pathway, to elaborate on the repair redundancy, as well as conditional models of the intermediate steps of BER.

Keywords: Base excision repair; DNA glycosylase; Mice

1. Introduction

Living cells are constantly exposed to environmental agents and endogenous processes that damage DNA. DNA lesions also accumulate spontaneously due to the chemical instability of DNA. Approximately 200 cytosines undergo deamination and 180 guanines oxidize to 8-oxo-deoxyguanine (8-oxoG) per mammalian cell per day. In addition, several thousand bases are lost due to spontaneous depurination [1].

The majority of the spontaneous lesions described above are removed via the base excision repair (BER) pathway. This pathway is highly conserved and is believed to represent an ancient defense mechanism, which counteracts the spontaneous decay of DNA [1,2]. Over the past 15 years, considerable progress has been made towards understanding the molecular genetics of BER. The specificity of BER is determined by the DNA glycosylase that initiates the repair pathway. Each DNA glycosylase is specific to a limited number of damaged bases [3,4]. The DNA glycosylase cleaves the N–C1′ glycosylic bond between the base and the deoxyribose. This results in the release of the damaged base, leaving an abasic (apurinic/apyrimidic) AP-site which is cytotoxic and mutagenic and which must be processed further. The mortality of gene-targeted mice in which enzymes involved in the downstream process of BER have been eliminated (Fig. 1) makes it apparent that the removal of these BER intermediates is crucial. DNA glycosylases are either monofunctional, only removing the base, or bifunctional, with an additional lyase activity cleaving 3′ of the AP-site. All known DNA glycosylases directed against oxidized bases are bifunctional [5].

The discovery of a 5′-deoxyribo-phosphatase activity of DNA polymerase β (Polβ) [6] has allowed the in vitro reconstitution of the mammalian BER pathway

* Corresponding author. Tel.: +47 23073119; fax: +47 23074061.
E-mail address: elisabel@medisin.uio.no (E. Larsen).

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doi:10.1016/j.mrfmmm.2006.01.023

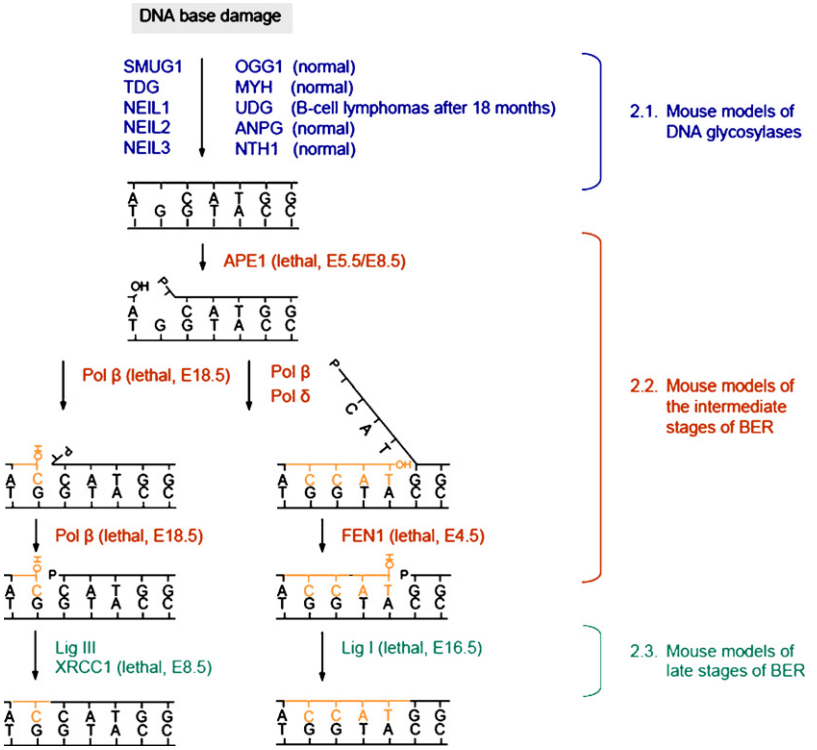

Fig. 1. Summary of gene-targeted knockout mice in BER. A simplified view of the branched pathways of BER. In the left pathway, a single nucleotide is replaced, whereas, several nucleotides are replaced in the right pathway. Regular AP-sites, resulting from spontaneous or glycosylase-initiated removal of the base, can be repaired via the single-nucleotide pathway, although a minor fraction is repaired via the right pathway. Oxidized or reduced AP-sites are removed via the right pathway. BER initiated by a DNA glycosylase with associated AP lyase activity, OGG1 or Nth1, is repaired slightly differently from the pathways illustrated. Gene-targeted knockout mice of the DNA glycosylases, ANPG, OGG1 and Nth1, have no apparent phenotype. The UDG knockout mice develop B-cell lymphomas after 18 months. Targeted disruptions of enzymes for processing key BER intermediates, highlighted in blue, all have a severe phenotype and are embryonically lethal. SMUG1, single-strand-specific monofunctional uracil-DNA glycosylase; TDG, thymine-DNA glycosylase; NEIL, Nei-like glycosylase; OGG1, 8-oxo-guanine glycosylase 1; MYH, adenine DNA glycosylase, UDG, uracil-DNA glycosylase; AAG, alkylpurine-DNA-N.glycosylase; Nth1, (mammalian) endonuclease III homolog 1; APE1, AP endonuclease 1; Pol, DNA polymerase; FEN1, flap endonuclease 1; Lig, DNA ligase; XRCC1, X-ray repair cross complementing 1.

using only four purified human enzymes [7]. A DNA glycosylase initiates the BER pathway via the removal of the damaged base, the AP endonuclease APE1 nicks the DNA strand at the AP-site, Polβ fills the gap and removes the 5′-phosphate sugar moiety; the repair is completed by the action of a DNA ligase [7]. This repair pathway is named short-patch BER. The Flap endonuclease 1 (FEN1)-dependent long-patch BER has since been reconstituted using purified human enzymes in vitro; in this case the FEN1 enzyme is required in addition to those described for the short-patch pathway [8,9]. The choice of sub-pathway in BER depends on whether the 5′-deoxyribose phosphate (dRP) intermediate can be efficiently removed by the activity of the Polβ lyase, to yield a 5′-phosphorylated DNA strand, capable of serving as a substrate for DNA, thereby displacing the dRP-containing strand. A DNA ligase seals the nick [8].

The metabolic profiles of different tissues vary considerably and tissues are exposed to varying levels of DNA damaging agents. Transgenic mice with reporter genes such as *LacZ* and *LacI* have been used to study and quantify spontaneous and induced mutagenesis in vivo. The results of these studies indicate that mutation frequency varies considerably with tissue type [10] and developmental stage [11] and that DNA damage accumulates at different rates in different tissues. However, it is unclear whether these differences reflect tissue-specific variations in the amount of DNA damage produced, or in DNA repair capacity [12].

Most of the genes coding for BER enzymes (only the core enzymes involved directly in the BER pathway are described as BER enzymes in this review) have been targeted for the generation of knockout mice [13]. The core BER enzyme pathways, as well as the gene-targeted mice produced, are illustrated in Fig. 1. These knockout