Mechanisms of Ageing and Development xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Mechanisms of Ageing and Development

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

Base excision repair in the mammalian brain: Implication for age related neurodegeneration

Q1 Peter Sykora, David M. Wilson III, Vilhelm A. Bohr *

Q2 *Laboratory of Molecular Gerontology, National Institute on Aging Intramural Research Program, 251 Bayview Boulevard, Suite 100, Baltimore, MD 21224, United States*

ARTICLE INFO

Article history:
Available online xxx

Keywords:
BER
Neurodegeneration
DNA repair
Aging

ABSTRACT

The repair of damaged DNA is essential to maintain longevity of an organism. The brain is a matrix of different neural cell types including proliferative astrocytes and post-mitotic neurons. Post-mitotic DNA repair is a version of proliferative DNA repair, with a reduced number of available pathways and most of these attenuated. Base excision repair (BER) is one pathway that remains robust in neurons; it is this pathway that resolves the damage due to oxidative stress. This oxidative damage is an unavoidable byproduct of respiration, and considering the high metabolic activity of neurons this type of damage is particularly pertinent in the brain. The accumulation of oxidative DNA damage over time is a central aspect of the theory of aging and repair of such chronic damage is of the highest importance. We review research conducted in BER mouse models to clarify the role of this pathway in the neural system. The requirement for BER in proliferating cells also correlates with high levels of many of the BER enzymes in neurogenesis after DNA damage. However, the pathway is also necessary for normal neural maintenance as larger infarct volumes after ischemic stroke are seen in some glycosylase deficient animals. Further, the requirement for DNA polymerase β in post-mitotic BER is potentially more important than in proliferating cells due to reduced levels of replicative polymerases. The BER response may have particular relevance for the onset and progression of many neurodegenerative diseases associated with an increase in oxidative stress including Alzheimer's.

1. Introduction

The brain is protected from many exogenous forms of DNA damage by the blood–brain barrier. It is probable that the majority of the DNA damage encountered by the brain is the result of toxic byproducts of normal cellular respiration. This endogenous source of oxidative DNA damage may be particularly high in the brain, correlating with its large oxygen demands. The human brain consumes as much as 50% of the arterial oxygen provided by the lungs despite representing on average only 2% of the total weight of the body (Magistretti and Pellerin, 1996). This oxygen is used to maintain a high metabolic rate required for the electrochemical transmissions between neurons and associated neural cells and also for continuous cell maintenance. The high metabolic rate inadvertently creates reactive oxygen species (ROS), volatile molecules such as superoxide anions, hydroxyl radicals and hydrogen peroxide. These molecules are able to damage cellular components including genetic material in the nucleus and mitochondria, a fundamental aspect of the oxidative stress and mitochondrial theories of aging and the evolution of carcinogenesis. Considering the longevity of neurons coupled with their inability to replicate, continuous repair of DNA to maintain genomic integrity is essential for neuronal survival and normal neural function throughout the lifespan of an organism.

The DNA repair field has been dominated by research utilizing proliferating cells spurred primarily by investigators in the field of carcinogenesis. However, experiments conducted in post-mitotic cells and neural tissues have identified substantial differences in DNA repair between proliferating and non-proliferating cells (Akbari et al., 2009; Wei and Englander, 2008). DNA repair in neurons appears to rely heavily on base excision repair (BER) but also utilizes non-homologous end joining (NHEJ) in the absence of homologous recombination. BER is the primary DNA repair pathway for the different, non-bulky forms of oxidative base modifications caused by ROS, as well as abasic sites and single-strand breaks that arise in DNA spontaneously, *via* the attack of ROS, or as intermediates during the repair response. The pathway is highly conserved amongst vertebrates and its importance can be extrapolated from the embryonic lethality of homozygous null murine models of many of the core BER enzymes (Fig. 1). BER consists of three sub pathways: short patch BER (SP-BER) (Fig. 2a), comprised primarily of enzymes dedicated exclusively to DNA repair; long patch repair (LP-BER) (Fig. 2a), comprised of repair as well as replication proteins; and single stranded break repair

Q3 * Corresponding author. Tel.: +1 410 558 8162; fax: +1 410 558 8157.
E-mail address: vbohr@nih.gov (V.A. Bohr).

0047-6374/$ – see front matter © 2013 Published by Elsevier Ireland Ltd.
http://dx.doi.org/10.1016/j.mad.2013.04.005

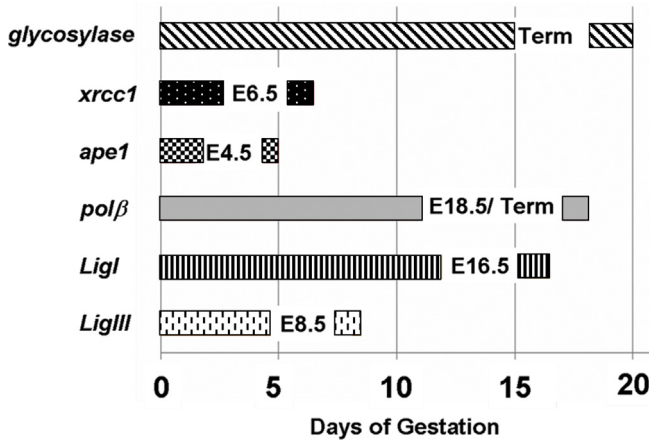

Fig. 1. Embryonic lethality of homozygous knockout mice. Only mice null for glycosylases are viable. All core BER enzymes are embryonically lethal. *polβ* mice may develop to term but are smaller than wild type littermates and have no induction of breathing response with death occurring shortly after birth (E = embryonic day).

(SSBR), an attenuated version of SP-BER that engages specialized termini "clean-up" proteins. SP-BER/SSBR are the major BER pathways in the brain, with residual LP-BER activity present in neuronal cells, yet at a reduced level in comparison to proliferating cells (Akbari et al., 2009; Wei and Englander, 2008).

BER of an apurinic/apyrimidinic site (AP site) can be completed with as few as three BER enzymes, AP endonuclease (APE1), DNA polymerase β (Polβ) and DNA ligase (either I or III). Processing of a damaged base moiety requires the additional activity of one of the range of substrate specific DNA glycosylase enzymes. Despite the relative simplicity of BER compared to NHEJ, our knowledge of the pathways in the brain remains limited. The objective of this article is to provide a comprehensive analysis of BER from research conducted using rodent models and human brain tissue. From this work it is evident that BER is indispensable for neural development during embryogenesis and is critical for normal function throughout life. In addition, decline of BER with age may accelerate age related cognitive dysfunction and the progression of neurodegenerative disease.

2. DNA glycosylases

Despite the broad range of substrates recognized, DNA glycosylase activity during BER is restricted to the same two or three enzymatic events. Initially, the glycosylase recognizes and binds to the modified base. Each glycosylase has evolved to process a subset of base modifications. Often the glycosylase can also process other similar lesion conformations, giving the glycosylase group a high degree of substrate overlap not seen in the subsequent steps of BER. The large number of glycosylases, 11 in total in humans, emphasizes this notion, and bi functional glycosylases responsible for the excision of DNA modifications associated with oxidative stress are of particular interest in the brain.

Three glycosylase groups process oxidative base lesions: 8-oxoguanine DNA glycosylase 1 (OGG1), endonucleases VIII-like (Neil) and endonuclease III-like (NTH). The substrate overlap between the glycosylases hinders identification of individual glycosylase activity, yet makes it possible to create viable homozygous null knockout mice. The phenotypes of these null animals are generally mild and only recently have researchers induced neural stress as a way of delineating the function of the glycosylases in the mammalian brain (Canugovi et al., 2012; Liu et al., 2011; Sejersted et al., 2011). Ogg1 null (*ogg1−/−*) mice were initially reported to only accumulate mutations after stress (Klungland et al., 1999). With this in consideration, it was proposed that OGG1 may be particularly important in the repair of oxidative lesions that rapidly accumulate after stroke, a

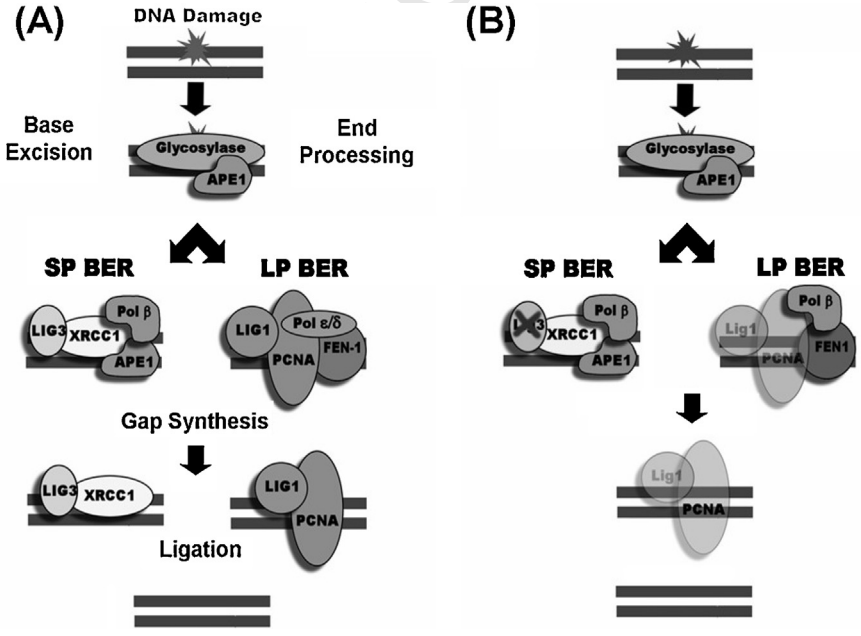

Fig. 2. (A) Diagrammatic representation of base excision repair (BER). The initial step of BER use the activity of the glycosylase enzymes and AP endonuclease 1 (APE1), to excise damage nucleotides and processes modified termini. The pathway can then proceed through one of the two sub pathways (short patch (SP-BER)) or (long patch (LP-BER)). SP-BER then uses the activity of DNA polymerase Beta (Polβ) to re-insert the correct nucleotide and DNA ligase 3 (Lig3)/XRCC1 to Reseal the phosphodiester backbone. In contrast LP-BER uses protein involved in replication including DNA polymerase delta and epsilon (Pol δ/ε) in conjunction with Flap endonuclease 1 (FEN-1) and proliferating cell nuclear antigen (PCNA) providing scaffolding for the complex. DNA ligase 1 (Lig1) provides the ligation activity. (B) Base excision repair in post-mitotic neurons. There is accumulating evidence that the repair pathway changes substantially after neural differentiation. Polβ takes a more prominent role after differentiation participating in both SP and LP-BER in the absence of the replicative polymerases. Lig3 does not participate in nuclear BER in post-mitotic cells. Ligation appears to be heavily dependent on Lig1 despite reduced levels of the protein in non-proliferating cells.

Please cite this article in press as: Sykora, P., et al., Base excision repair in the mammalian brain: Implication for age related neurodegeneration. Mech. Ageing Dev. (2013), http://dx.doi.org/10.1016/j.mad.2013.04.005