Mechanisms of Ageing and Development 129 (2008) 483–491

Contents lists available at ScienceDirect

Mechanisms of Ageing and Development

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

Review

DNA strand breaks, neurodegeneration and aging in the brain

Sachin Katyal, Peter J. McKinnon *

Department of Genetics and Tumor Cell Biology, St. Jude Children's Research Hospital, Memphis, TN 38105, USA

ARTICLE INFO

Article history:
Available online 25 March 2008

Keywords:
DNA damage
DNA repair
Nervous system
Aging
ATM
AOA1
SCAN1

ABSTRACT

Defective responses to DNA single- or double-strand breaks can result in neurological disease, underscoring the critical importance of DNA repair for neural homeostasis. Human DNA repair-deficient syndromes are generally congenital, in which brain pathology reflects the consequences of developmentally incurred DNA damage. Although, it is unclear to what degree DNA strand-break repair defects in mature neural cells contributes to disease pathology. However, DNA single-strand breaks are a relatively common lesion which if not repaired can impact cells via interference with transcription. Thus, this lesion, and probably to a lesser extent DNA double-strand breaks, may be particularly relevant to aging in the neural cell population. In this review we will examine the consequences of defective DNA strand-break repair towards homeostasis in the brain. Further, we also consider the utility of mouse models as reagents to understand the connection between DNA strand breaks and aging in the brain.

1. Introduction

The mammalian nervous system is formed through continual cycles of proliferation, differentiation and maturation to generate the large number of cell types required for function (Jacobsen, 1991). Although the human nervous system forms in a matter of months, neural tissues must be functional for decades of life, and the mature neurons bear the brunt of handling a lifetime of potential threats to the integrity of their DNA. Due to the substantial oxygen requirement for maintenance of CNS tissue, neurons must cope with oxidative and metabolic stress that can result in DNA strand breaks (Lombard et al., 2005; Barzilai, 2007; Chen et al., 2007). Accordingly, neurons require efficient DNA strand-break surveillance and repair mechanisms to deal with these types of lesions. Human neurological syndromes resulting from defects in DNA repair highlight the importance of multiple repair pathways for maintaining homeostasis in the brain (Rolig and McKinnon, 2000; McKinnon and Caldecott, 2007; Subba Rao, 2007). Hence, individuals who incur genetic mutations that inactivate these repair pathways show accelerated neuronal death, which can manifest as neurodegenerative disease. As most of these inherited syndromes are congenital, less is know about the effects of DNA repair deficiency during aging. Nonetheless, there are many studies reporting a link between aging and a decline in DNA repair activity (Intano et al., 2003; Lu et al., 2004; Vijg and Calder, 2004; Imam et al., 2006; Gorbunova et al., 2007; Rutten et al., 2007; Wilson and Bohr, 2007). However, the causal relationship between decreased DNA repair activity, increased mutations and an effect upon aging still has to be thoroughly evaluated. Clearly, understanding the role of DNA repair and aging in the brain will require suitable model systems and careful *in vivo* assessment of how the spatiotemporal changes in DNA repair capacity affects neural homeostasis.

This review will emphasize the requirement for DNA strand-break repair in the context of neural development. We will consider neurodegenerative diseases that are directly attributable to failure in strand-break responses and the importance of these pathways in the nervous system. We will also discuss the utility of mouse models of DNA repair deficiency as an important tool for understanding the impact of genomic instability in the brain, and how more refined genetic manipulation of the mouse will help us better understand the links between DNA repair deficiency and age-related disease of the CNS.

2. Neural development

Formation of mature neural tissue requires the expansion and differentiation of precursor cells into a variety of neural cell types that migrate, organize and stratify into distinct CNS structures. Fig. 1 illustrates the CNS with expanded views of two representative tissues, the retina and cerebellum, illustrating the laminar structure of these tissues. In many DNA repair syndromes the cerebellum is often a target, and as the cerebellum is responsible for motor coordination, ataxia is associated with these syndromes (Frappart and McKinnon, 2006; Lee and McKinnon, 2007).

* Corresponding author. Tel.: +1 901 495 2700; fax: +1 901 526 2907.
E-mail address: peter.mckinnon@stjude.org (P.J. McKinnon).

0047-6374/$ – see front matter © 2008 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.mad.2008.03.008

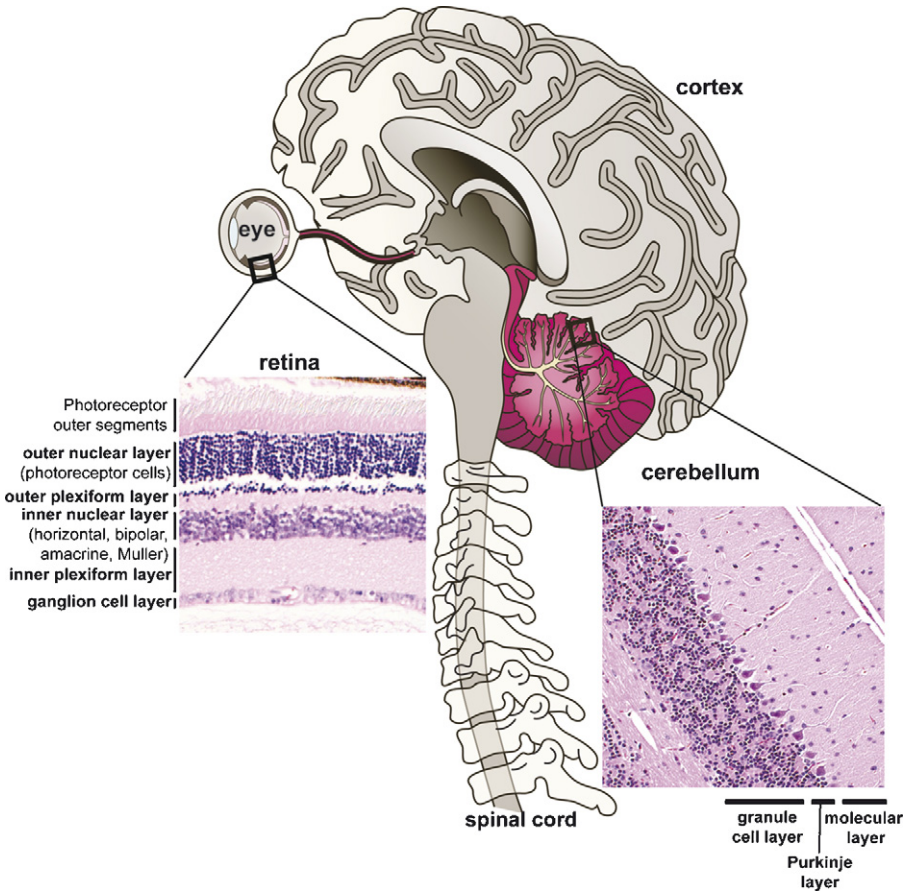

Fig. 1. The adult mammalian CNS. The mature nervous system contains a myriad of different cell types and tissues. DNA repair processes impact substantially during neural development leading to defective neurogenesis and development. However, less is known regarding the requirement for DNA repair processes in mature neural cell. Inset panels are hematoxylin and eosin stained retinal and cerebellar sections that show cell organization in these tissues. The retina is laminar in nature and cell types are stratified into three distinct nuclear layers: outer, inner and ganglion. The outer nuclear layer contains the photoreceptor (rods and cones) neurons. The inner nuclear layer contains various signal processing cell types: bipolar, horizontal, amacrine, interplexiform and the Müller glia. The ganglion cells carry the visual signal via its axons through the optic nerve and project onto the brain. The cerebellum is stratified into three primary layers: inner granule cell layer, the Purkinje cell layer and the molecular layer. Excitory sensory signals originating from the cerebellum are ultimately transmitted through granule-Purkinje synapses and out of the cerebellum through Purkinje neuron axons to affect normal control of movement.

Although the cerebellum only comprises 10% of the total brain mass, it contains approximately 50% of the neurons in the brain. The cerebellum is primarily composed of three general neuronal populations, the granule cells, the Purkinje cells and interneurons, with each type found in distinct cell layers; the inner granule layer, the Purkinje cell layer and interneurons which are found throughout the molecular layer and the inner granule layer (Fig. 1). During development, an external germinal layer is present and as cerebellar development progresses, granule neuron precursors generate granule cells that migrate inwards and populate the IGL as the external granule layer gradually diminishes (Goldowitz and Hamre, 1998; Wang and Zoghbi, 2001). The cell populations of the cerebellum are notable because granule cells are the most numerous neuronal cell types in the brain, while Purkinje cells are amongst the largest neuronal cell type in the brain. The outer molecular layer consists of interneurons (stellate and basket cells) together with Purkinje cell dendrites and parallel fibers arising from granule cells, making the molecular layer a synapse-rich area (Jacobsen, 1991; Goldowitz and Hamre, 1998). As the cerebellum serves primarily to control sensory–motor function, individuals with cerebellar neurodegenerative disorders, such as spinocerebellar atrophy and ataxia-telangiectasia (A-T), present with ataxia (impaired motor coordination) and eye-movement defects and speech disturbance (dysarthria) (Frappart and McKinnon, 2006; Limperopoulos and du Plessis, 2006).

While the cerebellum is often affected in diseases associated with DNA strand-break repair, progressive widespread neurodegeneration also occurs. In many cases these progressive changes are a later event than the effects upon the cerebellum. The likely scenario is that the cerebellum and perhaps granule cells in particular are very susceptible during postnatal neurogenesis to DNA damage. Furthermore, as defects in the cerebellum generally present as ataxia, an obvious movement disorder, this may cause milder cortical defects to be initially over-looked. As will be discussed later, mice with defective DNA strand-break repair further reveal the cerebellum as a primary target in the nervous system.

3. Repair of DNA strand breaks

DNA strand breaks can occur as either single-strand breaks (SSBs) or double-strand breaks (DSBs) and biochemically distinct pathways repair these lesions. DNA DSBs are repaired by either non-homologous end-joining (NHEJ) or homologous recombination (HR), while SSBs are repaired by the DNA SSB repair (SSBR) pathway (Caldecott, 2003; Lieber et al., 2003; West, 2003; Wyman and Kanaar, 2006; Helleday et al., 2007). In the nervous system DNA strand breaks can arise endogenously from normal cellular metabolism, during DNA replication or from exogenous agents such as ionizing radiation or chemicals in the environment. In differentiated neurons that do not divide, DNA DSBs clearly occur