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THE CASE FOR 8,5′-CYCLOPURINE-2′-DEOXYNUCLEOSIDES AS ENDOGENOUS DNA LESIONS THAT CAUSE NEURODEGENERATION IN XERODERMA PIGMENTOSUM

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Abstract—Patients with the genetic disease xeroderma pigmentosum (XP) lack the capacity to carry out a specific type of DNA repair process called nucleotide excision repair (NER). The NER pathway plays a critical role in the repair of DNA damage resulting from ultraviolet (UV) radiation. A subset of XP patients develops a profound neurodegenerative condition known as XP neurological disease. Robbins and colleagues [Andrews A, Barrett S, Robbins J (1978) Xeroderma pigmentosum neurological abnormalities correlate with the colony forming ability after ultraviolet irradiation. Proc Natl Acad Sci U S A 75:1984–1988] hypothesized that since UV light cannot reach into the human brain, XP neurological disease results from some form of endogenous DNA damage that is normally repaired by the NER pathway. In the absence of NER, the damage accumulates, causing neuronal death by blocking transcription. In this manuscript, I consider the evidence that a particular class of oxidative DNA lesions, the 8,5′-cyclopurine-2′-deoxynucleosides, fulfills many of the criteria expected of neurodegenerative DNA lesions in XP. Specifically, these lesions are chemically stable, endogenous DNA lesions that are repaired by the NER pathway but not by any other known process, and strongly block transcription by RNA polymerase II in cells from XP patients. A similar set of criteria might be used to evaluate other candidate DNA lesions responsible for neurological diseases resulting from defects in other DNA repair mechanisms as well. **© 2006 IBRO. Published by Elsevier Ltd. All rights reserved.**

Key words: DNA repair, Parkinson's disease, transcription, dopamine, cockayne syndrome, DeSanctis-Cacchione syndrome.

The DNA in our cells is constantly being damaged by endogenous sources such as oxygen radicals, as well as by environmental factors such as mutagenic chemicals and radiation. Fortunately, all cells are protected from these types of damages by an array of DNA repair pathways. A priori, it would be assumed that the major medical outcome of hereditary deficiencies in DNA repair processes would be an increased risk of cancer. Indeed there is an increased risk of cancer in several known DNA repair deficiencies including xeroderma pigmentosum (XP), Fanconi anemia, and hereditary non-polyposis colon cancer (Friedberg et al., 2005). However, it is now clear that the other major clinical manifestation of hereditary DNA repair deficiency is neurological disease, as discussed by other contributors to this special issue.

The focus of this manuscript is to discuss the neurological disease in patients with XP, the first example of a neurological disease associated with defective DNA repair (Andrews et al., 1978). I will first review the clinical and neuropathological characteristics of XP neurological disease, as well as the evidence that it results from defective nucleotide excision repair (NER). I will then discuss the evidence that a specific class of oxidatively-induced DNA lesions, the 8,5′-cyclopurine-2′-deoxynucleosides (cyclopurine-deoxynucleosides), are currently the best candidates for endogenous DNA lesions that are responsible for neurological disease in XP patients, and the clinical implications of this hypothesis. Finally, I will briefly consider the relevance of cyclopurine-deoxynucleosides in individuals with normal NER.

XP AND XP NEUROLOGICAL DISEASE

XP is a rare genetic disorder characterized by extreme sensitivity of the skin to sunlight, and a dramatically increased risk of skin cancer on sun-exposed areas of the body. XP can result from mutations in any of eight genes, denoted *XPA–G* and *V*. Patients with mutations in an individual XP gene are considered to be in a complementation group. For example, patients with mutations in the *XPA* gene are said to be in complementation group A. Cells from patients in complementation groups A through G are defective in NER, the main DNA repair pathway for ultraviolet (UV) light-induced DNA damage, whereas group V patients lack a specific type of DNA polymerase that can bypass mutagenic DNA damage resulting from UV light (Friedberg et al., 2005; Wattendorf and Kraemer, 2005).

Approximately 20% of XP patients worldwide develop a pattern of neurological abnormalities referred to as XP neurological disease (Robbins et al., 1991; Rapin et al., 2000). In the past, any XP patient with neurological abnormalities was described as having DeSanctis-Cacchione syndrome (DCS) (De Sanctis and Cacchione, 1932). At present, however, the term DCS is reserved for XP patients with severe neurological disease as well as dwarfism

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Abbreviations: BER, base excision repair; CS, Cockayne syndrome; CSF, cerebrospinal fluid; cyclo-dA, 8,5′-cyclo-2′-deoxyadenosine; Cyclopurine-deoxynucleoside, 8,5′-cyclopurine-2′-deoxynucleoside; DCS, DeSanctis-Cacchione syndrome; GC-MS, gas chromatography–mass spectrometry; HVA, homovanillic acid; JNK, c-Jun N-terminal kinase; MAO, monoamine oxidase; NER, nucleotide excision repair; PdG, propano-deoxyguanosine; Pol II, RNA polymerase II; TH, tyrosine hydroxylase; UV, ultraviolet; XP, xeroderma pigmentosum; 8-oxo-dG, 8-oxo-2′-deoxyguanosine.

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and immature sexual development (Wattendorf and Kraemer, 2005; see also below).

The signs and symptoms of XP neurological disease include peripheral neuropathy, sensorineural deafness, microcephaly, cerebral dysfunction, ventricular dilation, cortical atrophy, basal ganglia and cerebellar disturbances (Robbins et al., 1991). Progressive loss of tendon stretch reflexes and deteriorating hearing are required for a diagnosis of XP neurological disease (Rapin et al., 2000). The earliest signs of XP neurological disease are reduced tendon reflexes, most likely resulting from degeneration of the peripheral nervous system, and ataxia. As the disease progresses, the ataxia becomes worse and other motor abnormalities occur, eventually resulting in the patient becoming wheelchair bound. The patients subsequently experience progressive cognitive decline and dementia.

Robbins et al. (1991) have classified several different forms of XP neurological disease, depending upon the age of onset, which are in turn dependent on the specific mutation(s) that the patient inherited. In Japanese XPA patients, the onset and severity of neurological disease, including the age at which the patient will lose the ability to walk, can be accurately predicted from the patients' mutations (Maeda et al., 1995).

NEUROPATHOLOGY IN XP NEUROLOGICAL DISEASE

The results of several neuropathological examinations of patients with XP neurological disease have been published (Yano, 1950; Reed et al., 1965; Roytta and Antitnen, 1986; Itoh et al., 1999; Hayashi et al., 2004), and the description below is a summary of these studies.

At the gross level, the dominant feature of XP neurological disease is atrophy of the brain, spinal cord, and peripheral nervous system. The atrophy can be very severe, with loss of up to 40% of the brain tissue mass. At the microscopic level, the dominant observation is that of neuronal loss in different regions of the brain, as described below. Because this loss of neurons occurs in the absence of any other obvious causative processes, such as amyloid plaques, or Lewy bodies, it is considered to be a primary neurodegeneration.

While neuronal loss is widespread in the brains of XP patients, it is not uniform. Neuronal loss is prominent in cerebral cortex, where large neurons appear to be more strongly affected than smaller neurons. The number of large neurons is also reduced in the basal forebrain (i.e. the nucleus basalis of Meynert and substantia innominata). Neuronal loss also occurs in the hippocampus, and is prominent in the striatum (particularly the caudate nucleus) where the number of large neurons is reduced more than smaller neurons. While neuronal loss was observed in the anterior thalamic nucleus, other thalamic and hypothalamic nuclei were reported to appear normal, both in size and number (Yano, 1950), although other authors (Roytta and Antitnen, 1986) describe a light accumulation of lipofuschin granules in the neurons in these areas.

In the midbrain, all authors have observed that neurons in the substantia nigra and locus coeruleus are very severely affected. Yano (1950) describes the locus coeruleus as "macroscopically indistinguishable" in the brains of the XP patients he examined. Consistent with these observations, the levels of the dopamine metabolite homovanillic acid (HVA) in the cerebrospinal fluid (CSF) from an XP patient were reduced by over 95% (Roytta and Antitnen, 1986). These observations indicate that monoamine producing neurons are particularly susceptible to degeneration in XP. Possible reasons for this are discussed below (see Fig. 3).

Neuronal loss is severe in some brainstem nuclei but not in others (Hayashi et al., 2004). In the cerebellum, Purkinje cells are significantly affected whereas granule neurons are largely spared. Large neurons are preferentially affected in the spinal cord, and in dorsal root ganglia. The pathology in the spinal cord has been described as similar to that of patients with Friedreichs ataxia (Yano, 1950).

DIFFERENCES IN NEUROPATHOLOGY BETWEEN XP AND COCKAYNE SYNDROME (CS)

CS is a rare neurodevelopmental disorder characterized by sun sensitivity, as well as abnormal "bird-like" facies, severe cachectic dwarfism, and signs of premature aging (Rapin et al., 2000; Friedberg et al., 2005). Pure CS, i.e. CS without the additional clinical features of XP, results from mutations in the *CSA* or *CSB* genes, whereas certain mutations in the *XPB*, *XPD*, or *XPG* genes result in a disease with the combined features of CS and XP (Friedberg et al., 2005). For further discussion of XP and CS, see the contribution by Kraemer in this volume.

XP and CS are often grouped together as related diseases, due to the overlapping sun sensitivity phenotypes, as well as the role of the CS proteins in transcription-coupled NER (Friedberg et al., 2005). However, it is important to emphasize that even though patients with both diseases show neurological abnormalities, the specific nature of the neuropathologies is qualitatively different. In particular, the brains of CS patients show an unusual type of white matter loss that has been characterized as dysmyelination or tigroid leukodystrophy (Brumback et al., 2004). This specific type of pathology is not observed in XP. In addition, calcification of the basal ganglia and other regions of the brain is observed in CS, but not in XP (Leech et al., 1985; Rapin et al., 2000).

CAN DCS RESULT FROM MUTATIONS IN THE CSB GENE?

As noted above, the term DCS refers to a very severe form of XP neurological disease (De Sanctis and Cacchione, 1932). In light of this, the report that two brothers who were described as having DCS (Greenhaw et al., 1992) had inherited mutations in the *CSB* gene (Colella et al., 2000) was surprising. However, the clinical description of these

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