Neurodegeneration in xeroderma pigmentosum

The inability to repair damage to DNA clearly can have effects on post-mitotic neurons and cause severe CNS symptoms. Ataxia telangiectasia (A-T), ataxia oculomotor apraxia type 1 (AOA1) and spinocerebellar ataxia with axonal neuropathy (SCAN1) all show progressive neurodegeneration. While it is known that these disorders show defective DNA double or single strand break repair, the precise mechanism of the neurodegeneration is still a mystery (reviewed in McKinnon and Caldecott, 2007). For these and other disorders like Parkinson’s disease, oxidative stress may play an important role in damaging the neuronal DNA. In the case of xeroderma pigmentosum (XP), a very rare recessively inherited skin disorder showing predisposition to skin cancer as a result of a severe sensitivity to UV light, neurodegeneration is perhaps an unexpected feature. Nevertheless, this has been known for many years (Andrews et al., 1978; Kraemer et al., 1987).

Unravelling the function of the genes causing XP was important in understanding the process of nucleotide excision repair (NER), one of several processes involved in repairing damaged DNA (reviewed in Lehmann, 2003; Cleaver, 2005). NER is particularly relevant to the repair of thymine dimers caused by UV light. The cellular response to the thymine dimer involves its removal and replacement with normal nucleotides. A series of steps is required starting with recognition of the damage, followed by unwinding of the DNA at the site of the damage, cutting the DNA either side of the damaged segment, removing it, replacing the correct nucleotides, and finally ligating the new sequence. In total, seven genes, XPA–XPG, are involved in this process. Remarkably, mutation of any one of these genes results in XP. Some (XPA and XPC) are frequently mutated in XP and others (e.g. XPG), rarely. The level of the defect in repair is also different between genes, with mutation of XPA resulting in the most deficient repair. The skin tumours in XP are believed to arise as a result of failure to remove dimers, the insertion of random bases in daughter DNA strands during replication and thereby introducing mutation.

For the repair process, recognition of the thymine dimer is the important initiating step, facilitated by the product of the XPC gene—at least this is the case for DNA that is not in the process of being transcribed, termed global genome NER (GG-NER). The XPC gene product is restricted to GG-NER. In contrast, the recognition of a dimer in transcribing DNA occurs through a second pathway termed transcription coupled repair (TCR) NER. The XPA protein is required for both GG-NER and TCR-NER and indeed genes XPB and XPD–XPG, are also common to the two sub pathways. Importantly, however, both XPA and XPC are involved only in NER whereas other XP genes (e.g. XPB and XPD) have additional roles in the transcription process itself. Mutation of both XPC and XPA genes is associated with skin cancer. This risk is stronger with XPC whereas, in contrast, it has been known for some time that mutation of the XPA gene is more closely associated with neurodegeneration (Andrews et al., 1978; Kraemer et al., 1987). This is all very interesting because XPA is strictly a repair gene; the implication being that lack of repair is the cause of the neurodegeneration. In contrast, absence of neurological abnormalities in the XPC patients may be an indication that an intact transcription coupled NER is required for neuronal protection. Another group of XP patients (XPD and XPG mutants) also show neurodegeneration, but this is probably linked to the role of these genes either as part the transcription factor TFIIH or involvement in its stability (Friedberg and Wood, 2007).

In this issue of Brain, Anu Anttinen and colleagues describe prospectively the natural history of the neurological disease in 16 Finnish patients with XP—10 XP-A, 2 XP-C, 2 XP-G and two unassigned to a complementation group—over 2–23 years. The first clinical sign in all XP cases was severe sunburn, noticed before the age of 12 months although in only two cases did this lead to a diagnosis of XP. Skin tumours occurred earlier in the XP-C patients than in the XP-A patients. Over half of the XP-A patients had no skin tumours and neither of the XP-G patients had skin tumours.

As expected, the two XP-C patients were neurologically and cognitively unaffected although, curiously, there was some evidence for brain atrophy. Of the 10 XPA patients, 9 were homozygous for the same R228X mutation providing an opportunity for interesting comparisons between individuals of different ages. All had short stature and showed microcephaly. Normal development occurred until the age of 2 years. The first neurological signs occurred before the age of 8 years. In all cases, the presentation was with mild cognitive impairment. Each had learning difficulties; all showed a degree of diffuse encephalopathy. Then followed cerebellar signs, dysarthria, swallowing difficulties, problems of balance and lower limb ataxia and, later, neuropathy. Choreoathetoid movements were noted in early adulthood. Corticospinal involvement occurred in the third decade and cognitive impairment became severe. Seven patients died, all from pneumonia,
with a median age of 33 years. The two XP-G patients had only sensorineural hearing loss and peripheral neuropathy. Imaging invariably revealed general brain atrophy, including involvement of the brainstem and cerebellum that was mild in XP-C patients and moderate to severe in the XP-A patients.

The 'sixty four thousand dollar question' is the nature of the damage to the CNS that causes neurogeneration in so many disorders, in this instance patients with XP-A bearing in mind that UV light cannot reach the brain. It is most likely that there are some forms of oxidative damage for which NER is also the repair pathway, just as there are likely to be other forms where resolution will involve DNA strand break repair. There has been considerable speculation on the nature of the DNA lesion associated with neurodegeneration in XP including the suggestion that oxidative cyclopurine adducts are important (Brooks, 2007). Interestingly, so far, the availability of XP animal models has not helped in solving the problem. However, hopefully, the pressure to understand the role of oxidative damage in more common disorders such as Parkinson’s disease will speed the process of understanding the role of oxidative damage, more generally, in neurodegeneration.

References