Molecular Characterisation of Single-Strand Break Repair and Related Responses and their Role in Neuroprotection

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Title of project or programme

Title of PI	Molecular Characterisation of Single-Strand Break Repair and Related Responses and their Role in Neuroprotection

Principal Investigators of project/programme grant

Title	Forname	Surname	Institution	Country
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- United Kingdom

Source of funding information

Medical Research Council

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1958963.23

Start date of award

01-03-2007

Total duration of award in months

60

The project/programme is most relevant to

- Neurodegenerative disease in general

Research abstract in English

Single-strand breaks (SSBs) arise from a variety of sources including oxidative stress and are the commonest DNA lesions arising in cells (tens of thousands per cell per day). If not repaired, SSBs

can block transcription and DNA replication and lead to genetic instability and cell death. Strikingly, recent work from my laboratory has identified that two proteins associated with hereditary neurodegenerative disease are intimate components of the single-strand break repair (SSBR) machinery, and that cells from one of these diseases possess a major defect in chromosomal SSBR. We have thus recently proposed that SSBR is critical for genetic integrity and survival in neurons, and that this process is vital for normal neurological function. These observations also raise the intriguing possibility that SSBR capacity is an aetiological factor not only for pathological neurological conditions but also for normal human ageing. In the current proposal, we will identify and characterise novel polypeptide components of SSBR and related processes to advance and extend our understanding of this critical process. To achieve this we will employ a combination of genetic, biochemical/proteomic, and cellular approaches, and also implement two new techniques that we are developing. The latter will allow us to characterise, for the first time, SSBR at a site-specific chromosomal SSB (e.g. using ChIP analyses) and to dissect this process within a context of defined chromatin structure. In addition, we will test directly and unambiguously our hypothesis that SSBR is critical for normal neurological function. To achieve this, we will examine the importance of SSBR for genetic integrity and cell survival in primary neurons and for normal neurological function in vivo, using mouse model systems.

Keywords
Lay summary
In which category does this research fall?

- Basic research