Sir, We are grateful for the opportunity to respond to the correspondence from Oegema et al. (2013) and we thank the authors for their interest in our recent review article discussing the three known neurological disorders associated with defective single strand break repair, namely ataxia oculomotor apraxia 1 (AOA1), spinocerebellar ataxia with neuronal neuropathy 1 (SCAN1) and microcephaly, early-onset, intractable seizures and developmental delay (MCSZ) (Reynolds and Stewart, 2013a). A focus of our review was to highlight the different neurological pathologies associated with these three different DNA repair deficiency disorders and to discuss possible molecular causes underlying why patients with AOA1 and SCAN1 present with progressive cerebellar degeneration (Date et al., 2001; Moreira et al., 2001; Takashima et al., 2002), whereas those with MCSZ primarily exhibit microcephaly without any evidence of neuronal degeneration (Shen et al., 2010). We hypothesized that the differential neuropathologies associated with these three different DNA repair deficiency disorders and to discuss possible molecular causes underlying why patients with AOA1 and SCAN1 present with progressive cerebellar degeneration (Date et al., 2001; Moreira et al., 2001; Takashima et al., 2002), whereas those with MCSZ primarily exhibit microcephaly without any evidence of neuronal degeneration (Shen et al., 2010). We hypothesized that the differential neuropathologies associated with these three different DNA repair deficiency defects present in combination with the relative frequency with which the specific DNA lesions repaired by the gene product mutated in these syndromes are likely to occur during nervous system development and maintenance. PNKP, which is mutated in MCSZ, is a critical end-processing factor involved in the repair of both single and double DNA strand breaks. It is postulated that any defect resulting in elevated levels of unrepairred DNA single strand breaks in rapidly proliferating neural progenitor cells would also lead to increased formation of DNA double strand breaks and as such, a combination of compromised repair of single strand and double strand breaks would result in increased cell death and the development of microcephaly. In contrast, APTX and TDP1, which are mutated in AOA1 and SCAN1, respectively, function during single strand break repair to correct abortive ligation or topoisomerase I cleavage intermediates that arise following attack of the DNA by reactive oxygen species. It is thought that these lesions arise very rarely and/or can be dealt with by redundant repair pathways active in cycling cells. As a consequence, deficiencies in the repair of these lesions do not have a pronounced affect on development of the brain and nervous system. However, it is likely that the accumulation of these rare unrepaired DNA lesions in the absence of APTX or SCAN1 trigger progressive neuronal cell death.

One puzzling aspect of this model is that as PNKP is a major factor for the processing of DNA termini following the induction of single strand breaks or oxidative damage, loss of its activity would be predicted to compromise DNA repair sufficiently in the developed brain that patients with MCSZ would also display cerebellar degeneration. Until recently, this was not the case. We reasoned that the hypomorphic nature of the PNKP mutations could retain sufficient residual 3’-phosphatase activity to prevent cerebellar degeneration; however, we agree that this explanation is not entirely satisfactory (Reynolds et al., 2012). The recent discovery of two brothers with a homozygous mutation in PNKP (T424Gfs48X) that exhibit both microcephaly and progressive cerebellar degeneration is consistent with the dual role for this enzyme in both single and double strand break repair (Poulton et al., 2013).

It is now evident that progressive cerebellar degeneration is a clinical symptom common to all three human genetic disorders associated with defective single strand break repair. In keeping with this, as noted by Oegema et al. (2013), mice in which the core SSBR factor XRCC1 has been conditionally deleted from the brain exhibit both microcephaly and also a loss of purkinje cells that results in ataxia (Lee et al., 2009). It is still unclear why the...
original cohort of patients with MCSZ identified did not exhibit any cerebellar degeneration, especially considering that some of these affected individuals share the same homozygous PNKP mutation (T424Gfs48X) with patients described by Shen et al. (2010). Given that considerable variation in clinical presentation as well as disease severity is frequently observed in many human disorders associated with a defective response to DNA damage (Reynolds and Stewart, 2013b), it is likely that this also occurs in patients with MCSZ. Although, the underlying reason for this is unknown, it is probably influenced by a number of additional genetic, environmental and/or epigenetic factors. However, as only two patients with MCSZ have been identified with cerebellar degeneration, it remains to be seen whether this neuropathology will be a clinical feature commonly exhibited by patients with PNKP mutations and only the identification of more patients with MCSZ will be able to address this.

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References


