Single-strand Breakage and Neurological Disease

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The DNA repair protein XRCC1 is required for the rapid repair of chromosomal DNA single-strand breaks (SSBs). XRCC1 is a scaffold protein that interacts with multiple enzymes (e.g., PARP1, PNKP, Polβ, APTX, Lig3) and promotes their stability and/or function. SSBs are amongst the most frequent DNA lesions arising in cells and if not repaired correctly can threaten both genetic stability and cell survival. Moreover, SSB repair defects are associated with hereditary neurodegeneration in humans, as illustrated by the genetic diseases ataxia oculomotor apraxia-1 (AOA1; mutated in APTX), spinocerebellar ataxia with axonal neuropathy-1 (SCAN1; mutated in TDP1), and microcephaly with early onset seizures (MCSZ; mutated in PNKP). Here, we describe for the first time a human patient with bi-allelic mutations in XRCC1. We describe the cellular and pathological consequences of XRCC1 loss in human and mouse brain and identify a molecular mechanism by which unrepaired SSBs trigger neuropathology. Collectively, these data establish the importance of XRCC1 protein complexes for normal neurological function and identify a possible therapeutic approach for treating DNA strand break repair-defective neurodegenerative diseases.