Abstract

DNA single-strand breaks (SSBs) are amongst the most frequent DNA lesions arising in cells and can threaten genetic integrity and cell survival, as indicated by the elevated genetic deletion, embryonic lethality and neurological disease observed when single-strand break repair (SSBR) is attenuated.

One of the proteins important for rapid repair of SSBs is XRCC1, which is a molecular scaffold protein that interacts with multiple DNA repair enzymes (e.g. PARP1, PNKP, POLβ, APTX, LIG3) and thus, promotes their stability and/or function. Defects in SSBR have been associated with hereditary neurodegeneration in humans, cerebellar ataxias and seizures. Here, I focus on genetic disease *spinocerebellar ataxia autosomal recessive-26 (SCAR26)*, which has been shown to be linked to mutations in *XRCC1*.

I investigate the amount of XRCC1 protein in *XRCC1*-defective cells and reveal that cells from patients with mutations in XRCC1 exhibit greatly reduced XRCC1 levels. I show that reduced levels of XRCC1 protein in cells correlate with the increasing number of endogenous SSBs, measured by quantification of ADP-ribose in the chromatin.

In addition, I confirm that the most endogenous SSBs arise in S phase of the cells cycle during replication. Moreover, I prove that the main sources of the endogenous SSBs in XRCC1-defective cells are not an aberrant Topoisomerase I activity-induced lesions, neither lesions, whose repair require the PNKP activity. Ultimately, I propose a hypothesis that unrepaired oxidative lesions are those, which might trigger the neurodegenerative disease associated with XRCC1 mutation.

Key words: XRCC1, SSB, SSBR, DNA damage, DNA damage repair pathway, neurodegeneration, ataxia