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Lamin A/C promotes DNA base excision repair.

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Abstract

The A-type lamins (lamin A/C), encoded by the LMNA gene, are important structural components of the nuclear lamina. LMNA mutations lead to degenerative disorders known as laminopathies, including the premature aging disease Hutchinson-Gilford progeria syndrome. In addition, altered lamin A/C expression is found in various cancers. Reports indicate that lamin A/C plays a role in DNA double strand break repair, but a role in DNA base excision repair (BER) has not been described. We provide evidence for reduced BER efficiency in lamin A/C-depleted cells (Lmna null MEFs and lamin A/C-knockdown U2OS). The mechanism involves impairment of the APE1 and POLβ BER activities, partly effectuated by associated reduction in poly-ADP-ribose chain formation. Also, Lmna null MEFs displayed reduced expression of several core BER enzymes (PARP1, LIG3 and POLβ). Absence of Lmna led to accumulation of 8-oxoguanine (8-oxoG) lesions, and to an increased frequency of substitution mutations induced by chronic oxidative stress including GC>TA transversions (a fingerprint of 8-oxoG:A mismatches). Collectively, our results provide novel insights into the functional interplay between the nuclear lamina and cellular defenses against oxidative DNA damage, with implications for cancer and aging.

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