OGG1 and MUTYH repair activities promote telomeric 8-oxoguanine induced senescence in human fibroblasts

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Telomeres are protective structures at the ends of chromosomes that safeguard genomic integrity and are essential for continuous cellular replication. DNA damage at telomeres poses a unique threat to genome stability, given the guanine-rich nature of telomeric sequences and their vulnerability to oxidative stress. Among the most prevalent lesions is 8-oxoguanine (8oxoG). OGG1 or MUTYH glycosylases initiate base excision repair (BER) by removing 8oxoG or a misinserted A opposite the lesion, respectively. While BER of 8oxoG is essential for maintaining genome integrity, its role at telomeres remains incompletely understood.

In an earlier study we discovered that targeted formation of 8oxoG at telomeres promotes premature cellular aging, characterized as cell senescence, which is an irreversible state of growth arrest. In this study, we investigated how BER activity modulates cellular responses to telomeric 8oxoG in human fibroblasts. We discovered that the loss or inhibition of OGG1, as well as the loss of MUTYH, partially mitigates premature senescence and associated proinflammatory responses induced by telomeric 8oxoG damage. Strikingly, the simultaneous deficiency of both glycosylases nearly abolished the growth arrest and telomere defects caused by telomeric 8oxoG, revealing a critical role for BER initiation in senescence signaling.

To probe the mechanism, we adapted and applied a novel microscopy-based technique to visualize and quantify DNA single-strand break repair intermediates specifically at telomeres in intact cells. Using this assay, we showed that BER activity promotes the accumulation of repair intermediates at telomeres, which interfere with telomere replication and trigger a DNA damage response.

PARP1 enzyme binds repair intermediates to recruit repair proteins and facilitate completion of the BER process. We further demonstrated that preventing BER initiation reduced PARP1 activation and conferred resistance to the synergistic effects of PARP inhibitors on telomeric 8oxoG-induced senescence. When subjecting the cells to chronic telomeric 8oxoG formation, we observed a surprising role for MUTYH in promoting senescence to prevent chromosomal instability from unrepaired damage.

Our findings reveal that although BER enzymes act to repair telomeric oxidative lesions, their activity can paradoxically drive senescence by generating toxic intermediates. By combining precise oxidative lesion targeting with single-strand break detection at telomeres, our study provides mechanistic insight into how the processing of oxidative damage at chromosome ends can promote cellular aging and aging-related phenotypes. This research was funded by the NIH (NIEHS, NCI, NINDS) and the Richard King Mellon Foundation.