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PII: S1568-7864(18)30072-7
DOI: https://doi.org/10.1016/j.dnarep.2018.04.001
Reference: DNAREP 2481

To appear in: *DNA Repair*

Received date: 10-4-2018
Accepted date: 10-4-2018

Please cite this article as: Shiladitya Sengupta, Chunying Yang, Muralidhar L.Hegde, Pavana M.Hegde, Joy Mitra, Arvind Pandey, Arijit Dutta, Abdul Tayyeb Datarwala, Kishor K.Bhakat, Sankar Mitra, Acetylation of Oxidized Base Repair-Initiating NEIL1 DNA Glycosylase Required for Chromatin Bound Repair Complex Formation in Human Genome Increases Cellular Resistance to Oxidative Stress, DNA Repair https://doi.org/10.1016/j.dnarep.2018.04.001

Acetylation of Oxidized Base Repair-Initiating NEIL1 DNA Glycosylase Required for Chromatin Bound Repair Complex Formation in Human Genome Increases Cellular Resistance to Oxidative Stress

Running title: Acetylation of NEIL1 is required for BER complex formation

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Highlights

- Human NEIL1 is acetylated by p300 at Lys 296-298 residues located in its disordered C-terminal domain.
- Although dispensable for NEIL1's activity, acetylation enhances the DG activity via enhanced product release.
- Acetylated NEIL1 (AcNEIL1) forms active repair complexes in chromatin, and cross talks with different chromatin factors including histone chaperones.
- Acetylation stabilizes NEIL1 repair complexes in chromatin, thereby protecting cells from oxidative stress.

Abstract

Posttranslational modifications of DNA repair proteins have been linked to their function. However, it is not clear if posttranslational acetylation affects subcellular localization of these enzymes. Here, we show that the human DNA glycosylase NEIL1, which is involved in repair of both endo- and exogenously generated oxidized bases via the base excision repair (BER) pathway, is acetylated by histone acetyltransferase p300. Acetylation occurs predominantly at Lys residues 296, 297 and 298 located in NEIL1's disordered C-terminal domain. NEIL1 mutant having the substitution of Lys 296–298 with neutral Ala lost nuclear localization, whereas Lys>Arg substitution (in 3KR mutant) at the same sites did not affect NEIL1's nuclear localization or chromatin binding, presumably due to retention of the positive charge. Although non-acetylated NEIL1 can bind to chromatin, acetylated NEIL1 is exclusively chromatin-bound. NEIL1 acetylation while dispensable for its glycosylase activity enhances it due to increased product release. The acetylation-defective 3KR mutant forms less stable complexes with various chromatin proteins, including histone chaperones and BER/single-strand break repair partners, than the wild-type (WT) NEIL1. We also showed that the repair complex with WT NEIL1 has significantly higher BER activity than the 3KR mutant complex. This is consistent with reduced resistance of non-acetylable mutant NEIL1 expressing cells to oxidative stress relative to cells expressing acetylable WT enzyme. We thus conclude that the major role of acetylable Lys residues in NEIL1 is to stabilize the formation of chromatin-bound repair complexes which protect cells from oxidative stress.