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Gene Section
Mini Review

NEIL1 (nei endonuclease VIII-like 1 (E. coli))

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Identity

Hugo: NEIL1
Other names: FLJ22402; FPG1; hFPG1; NEH1; NEI1
Location: 15q24.2

DNA/RNA

Description

The NEIL1 gene maps on chromosome 15q24.2 spanning 8,179bp. It contains 11 exons, and the orientation is plus strand.

Transcription

The transcript of 1,828bp, expressed in Brain, Liver, Lung, Kidney, Colon, and Stomach. The NEIL1 gene is up-regulated during S-phase.

Protein

Description

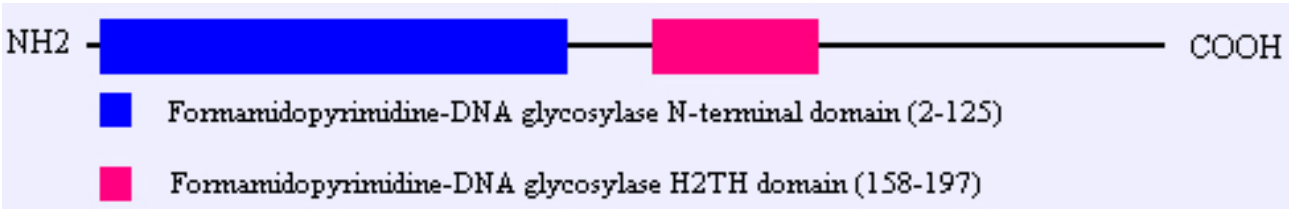
NEIL1 encodes 390 amino acids, theoretical molecular weight is 43684 Da, Formamidopyrimidine-DNA glycosylase N-terminal domain and Formamidopyrimidine-DNA glycosylase H2TH domain.

Localisation

Nucleus, centrosome, and mitotic condensed chromosomes.

Function

(1) Bifunctional DNA glycosylase and apurinic/apyrimidinic (AP) lyase that catalyzes beta- and delta-elimination reactions at the site of damaged base.
(2) Reported substrates: thymine glycol (Tg), 5-hydroxycytosine, 5-hydroxyuracil, 5,6-dihydrouracil, 5,6-dihydrothymine, 2,6-diamino-4-hydroxy-5-formamidopyrimidine (FapyG), 4,6-diamino-5-formamidopyrimidine (FapyA), 5-formyluracil, 5-hydroxymethyluracil, spiroiminodihydantoin (Sp), guanidinohydantoin, (Gh) and 8-hydroxyguanine.
(3) Since NEIL1 catalyzes beta- and delta-elimination reactions, the protein generates DNA strand breaks with 3' phosphate termini. In mammalian cells, this 3' phosphate is removed by polynucleotide kinase, but not by APE1. NEIL1 stably interacts with other BER proteins, DNA polymerase beta and DNA ligase III alpha.
(4) In mammalian BER, DNA glycosylases generate abasic (AP) sites, which are then converted to deoxyribo-5'-phosphate (dRP) and excised by a dRP lyase (dRPase) activity of DNA polymerase beta. Since NEIL1 also has dRPase activity, NEIL1 has a role as a backup dRPase in mammalian cells.
(5) NEIL1 has a repair activity for oxidized bases in single-strand DNA and bubble DNA, suggesting a possibility that NEIL1 is preferentially involved in repair of lesions in DNA bubbles generated during transcription and/or replication.
(6) Proteins that associate and stimulate the repair activity of NEIL1: a) The Werner syndrome protein (WRN), a member of RecQ family of DNA helicases, b) Rad9, Rad1, and Hus1 as individual proteins and as the 9-1-1 complex.
(7) The major DNA glycosylase for the excision of 8-hydroxyguanine is OGG1. In the repair of 8-ydroxyguanine by OGG1, after excising the base lesion, OGG1 remains bound to the resulting AP site and does not turn over efficiently. The APE1, which cleaves the phosphodiester bond 5' to the AP site, displaces the bound OGG1 and thus increases its turnover. NEIL1 stimulates turnover of OGG1 in a fashion similar to that of APE1, and carries out beta/delta- elimination at the AP site.



(8) Although OGG1 has limited activity on 8-hydroxyguanine lesion located in the vicinity of the 3' end of a DNA single-strand break, NEIL1 effectively excises the 3' end proximal 8-hydroxyguanine lesion. NEIL1 also effectively excises 5-hydroxyuracil lesions located in the proximity of the 3'-end of a DNA single-strand break.
(9) The NEIL1 gene is induced by reactive oxygen species.

Homology

Homo sapiens: NEIL2 (NP_659480, 20.1%), NEIL3 (NP_060718, 15.0%) using the CLUSTALW software.

Implicated in

Gastric cancer

Note: The following is the abstract of the paper by Shinmura K. et al. (Carcinogenesis, 2004). Oxidized DNA base lesions, such as thymine glycol (Tg) and 8-hydroxyguanine, are often toxic and mutagenic and have been implicated in carcinogenesis. To clarify whether NEIL1 protein, which exhibits excision repair activity towards such base lesions, is involved in gastric carcinogenesis, we examined 71 primary gastric cancers from Japanese patients and four gastric cancer cell lines for mutations and genetic polymorphisms of the NEIL1 gene. We also examined 20 blood samples from Chinese patients for NEIL1 genetic polymorphisms. Three mutations (c.82_84delGAG:p.Glu28del, c.936G > A and c.1000A > G:p.Arg334Gly) and two genetic polymorphisms were identified. When the excision repair activity towards double-stranded oligonucleotide containing a Tg:A base pair was compared among six types of recombinant NEIL1 proteins, p.Glu28del-type NEIL1, found in a primary case, was found to exhibit an extremely low activity level. Moreover, c.936G > A, located in the last nucleotide of exon 10 and detected in the KATO-III cell line, was shown to be associated with a splicing abnormality using an in vivo splicing assay. An immunofluorescence analysis showed that the wild-type NEIL1 protein, but not the truncated protein encoded by the abnormal transcript arising from the c.936G > A mutation, was localized in the nucleus, suggesting that the truncated protein is unlikely to be capable of repairing nuclear DNA. An expression analysis revealed that NEIL1 mRNA expression was reduced in six of 13 (46%) primary gastric cancer specimens that were examined. These results suggest that low NEIL1 activities arising from mutations and reduced expression may be involved in the pathogenesis in a subset of gastric cancers.

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