Table 2: The substrates specificities of NEILs

Name	Mono-/ bifurcate	Base	Substrates specificity	DNA
NEIL1	B	Pyrimidines/ purines	Sp, Gh, DHT, DHU, Tg, 5-OHC, 5-OHU, 8-oxoG, FapyG, and FapyA	ssDNA/ dsDNA
NEIL2	B	Pyrimidines/ purines	Sp, Gh, DHT, DHU, Tg, 5-OHC, 5-OHU, and 8-oxoG	ssDNA/ dsDNA
NEIL3	M/B	Pyrimidines/ purines	Sp, Gh, FapyG, and FapyA	ssDNA

Sp: spiroiminodihydantoin; Gh: guanidinohydantoin; DHT: 5,6-dihydrothymine; DHU: 5,6-dihydrouracil; FapyG: 2,6-diamino-4-hydroxy-5-formamidopyrimidine; FapyA: 4,6-diamino-5-formamidopyrimidine; 5-OHC: 5-hydroxycytosine; 5-OHU: 5-hydroxyruacil; Tg: thygly; 8-oxoG: 8-oxoguanine; ssDNA: single-stranded DNA; dsDNA: double-stranded DNA

cortex region is age-dependent and maximal in the middle-age. However, in the hippocampus, one of the neurogenic regions in the brain, mitochondrial NEIL1 is stable throughout a lifetime. By using a 5-OHdU containing bubble substrate, Gredilla *et al.*[26] found that mitochondrial NEIL1 activity showed an age-related change in the cortex with a significant peak at middle-age in the cortical region, but not in the hippocampus where no significant change occurred during the lifespan. The distinct age-dependent, subcellular- and tissue-distribution suggests that the role of NEIL1 is strongly connected to site-specific conditions.

In conclusion, the widespread expression of NEIL1in mammals demonstrated its unique role in the maintenance of gene integrity.

NEIL2 expression patterns

By using Northern analysis, NEIL2 was found to have the highest expression in the skeletal muscle and testis, moderate expression levels in the brain and heart and a very low level expression in placenta, lung, liver, kidney, and pancreas.[17] The same study also showed that NEIL2 mRNA level did not significantly change through the cell cycle and that NEIL2 was predominantly mitochondrially localized.[17] NEIL2 expression had also been detected in embryonic, neonatal, and adult rat brain and the expression level increased 1.5-2.5-fold in the mature rat brain compared to the embryonic brain, which is the same as NEIL1.[25] In the human brain, NEIL2 showed a widespread expression pattern in accordance with OGG1, NTH1, and NEIL1.[24] Rolseth *et al.*[24] also found that NEIIL2 had a similar expression pattern as NEIL1 by detecting expression of NEIL2 in mouse brain during postnatal development, but with a slightly increased expression with age. In summary, NEIL2 has a widespread expression pattern in human and rodent and the subcellular localization of NEIL2 is in mitochondria and in the nucleus. This distribution and tissue specificity of NEIL2 suggest that it may serve as a critical factor to maintain the integrity of the genome lifelong.

NEIL3 expression patterns

Compared to NEIL1 and NEIL2, The NEIL3 has a very distinct expression pattern.[18] Among all the human adult tissues, NEIL3 is only expressed at detectable levels in the thymus and testis, which indicates that NEIL3 might have a specialized function associated with proliferative capacity. Torisu *et al.*,[27] studied the expression level of NEIL3 in human but only found NEIL3 expression in thymus. In mouse tissue, NEIL3 mRNA was expressed in thymus, spleen, and bone marrow.[27] By developing NEIL3-null mice, Torisu found that NEIL3-null mice looked healthy for at least 24 weeks after birth. Furthermore, NEIL3-null male mice were viable and fertile. According to these findings, Torisu *et al.*[27] concluded that NEIL3 was not required for maintenance of testis function but had a potential function in the development of the hemopoietic system. In the central nervous system, NEIL3 mRNA expression has been investigated in different brain areas of human adults by Northern blot hybridization.[24] NEIL3 could not be detected in any brain region of adult humans. In contrast, by studying the expression of NEIL3 in mouse brain during postnatal development, NEIL3 transcripts can be observed in the subventricular zone (SVZ), hilus of the hippocampal formation, the rostral migratory stream, and the Purkinje cell of the cerebellum in P3 mice brain. In 1-month-old mouse brain, the NEIL3 was detected in layer V of the neocortex and only in a few cells in the SVZ and in the 1-year-old brain only in layer V of the neocortex. These results indicate that the expression of NEIL3 declines with age, and it is selectively expressed in brain regions associated with neurogenesis. NEIL3 expression has also been detected in regions rich in neurogenesis in the embryonic brain[28] and in two recent studies NEIL3-null models showed a decreased differentiation potential of neural stem cells.[29,30] NEIL3-null mice showed learning and memory deficits and reduced anxiety-like behavior, and synaptic irregularities in hippocampal neurons.[31] All together, these results suggest that NEIL3 may have a specific role in neurogenesis in the central nervous system.

The NEIL3 has been shown to be highly expressed in many tumor tissues, which supports the notion that NEIL3 might be associated with proliferation capacity.[32-34]

Regarding the subcellular localization of NEIL3, two studies have consistently found that NEIL3 is expressed in the cell nucleus.[18,27] Two additional

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