Ageing Research Reviews 118 (2026) 103129

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review article

The role and therapeutic potential of DNA glycosylases in Alzheimer's disease

Xia Zhao [a,1,*], Yingzhou Li [a,1], Ziyao Meng [a], Xiaoxia Xu [a], Linjie Chen [a], Qin Yu [a], Ruya Wang [a], Yiyu Ren [a], Fan Chen [a], Qi Ai [b], Yu Deng [b], Houming Yu [b], Jurui Wei [b], Guang Liang [a,c,*]

[a] *School of Pharmaceutical Sciences, Hangzhou Medical College, Hangzhou, Zhejiang 311399, China*
[b] *The First People's Hospital of Lin'an District, Affiliated Lin'an People's Hospital, Hangzhou Medical College, Hangzhou, Zhejiang 310014, China*
[c] *Chemical Biology Research Center, School of Pharmaceutical Sciences, Wenzhou Medical University, Wenzhou, Zhejiang 325035, China*

ARTICLE INFO

Keywords:
Alzheimer's disease
DNA glycosylases
Base excision repair
DNA damage
Therapeutic targets

ABSTRACT

The aging brain is highly vulnerable to oxidative genomic damage, the accumulation of which is a hallmark of Alzheimer's disease (AD). The base excision repair (BER) pathway, initiated by DNA glycosylases, serves as the primary guardian against such damage. This review synthesizes recent evidence revealing the dual and dynamic roles of key DNA glycosylases including OGG1, MUTYH, MPG, and members of the NEIL family in AD pathogenesis. Beyond canonical repair functions, these enzymes actively participate in core pathological processes including Aβ/tau toxicity, neuroinflammation, and neuronal death, with their activities modulated by the AD microenvironment. We evaluate the therapeutic strategies targeting these enzymes, highlighting emerging strategies like OGG1 agonists for early-stage repair enhancement and inhibitors for dampening maladaptive inflammation in later stages. Finally, we propose a precision medicine approach based on a deeper understanding of glycosylase biology in distinct brain cell types and disease stages, providing a theoretical foundation for DNA repair-targeted interventions in AD.

1. Introduction

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder and the leading cause of dementia worldwide, affecting over 50 million people globally with a projected increase to 152 million by 2050 (El Gaamouch et al., 2022). The global healthcare burden of AD is staggering, with US expenditures for individuals aged 65 and older with dementia expected to reach $384 billion in 2025(2025). AD is characterized by memory impairment, behavioral abnormalities, and cognitive decline (Wang et al., 2024), with core pathological hallmarks including senile plaques composed of Aβ aggregates, neurofibrillary tangles (NFTs) formed by hyperphosphorylated tau, synaptic loss, and neuronal death(Das, 2025; Götz et al., 2012). Aging is the strongest risk factor for AD, and genomic instability driven by accumulated DNA damage is a hallmark of the aging process(Brazel and Rao, 2004; Chu et al., 2022). Elucidating how the fundamental molecular pathways that link the aging process to the canonical pathological hallmarks of AD offers a promising frontier for understanding AD pathogenesis and identifying novel therapeutic targets.

Evidence indicates that genomic instability and DNA damage accumulation are central to brain aging(Lagunas-Rangel, 2022; López-Gil et al., 2023), contributing directly to cognitive impairment in AD and other neurological disorders (Delint-Ramirez and Madabhushi, 2025; Moneim, 2015). As post-mitotic cells with high metabolic activity, neurons are persistently vulnerable to reactive oxygen species (ROS), excitotoxicity, and transcription-associated damage(McKinnon, 2013; Yin and Yang, 2024). Failure to repair such damage compromises genomic integrity, triggering aberrant cell cycle re-entry, mitochondrial dysfunction, and ultimately irreversible neuronal loss (Chow and Herrup, 2015).

Among various DNA damage forms, 8-oxoG accumulation is a critical biomarker and neurotoxic agent in oxidative stress-induced neurodegeneration (Chiorcea-Paquim, 2022; Valavanidis et al., 2009). Its accumulation activates apoptotic effectors such as calpain and PARP, driving neuronal death - a hallmark event in neurodegenerative progression (Sheng et al., 2012). Consequently, downstream effectors like

* Correspondence to: School of Pharmaceutical Sciences, Hangzhou Medical College, Hangzhou, Zhejiang 310014, China.
E-mail addresses: xiazhao@hmc.edu.cn (X. Zhao), wzmcliangguang@163.com (G. Liang).
[1] These authors contribute equally to this work.

https://doi.org/10.1016/j.arr.2026.103129
Received 22 January 2026; Received in revised form 18 March 2026; Accepted 5 April 2026
Available online 7 April 2026
1568-1637/© 2026 Elsevier B.V. All rights reserved, including those for text and data mining, AI training, and similar technologies.

calpain and PARP are widely acknowledged as common therapeutic targets for multiple neurodegenerative diseases(Fujikawa, 2023; Hajnády et al., 2022). The BER pathway is the primary mechanism for repairing 8-oxoG and other single-base lesions, initiated by DNA glycosylases that act as "molecular sentinels" of genomic integrity (González-Díaz et al., 2024; Maynard et al., 2015; Nakabeppu, 2017). In AD patient brains, aberrant expression of DNA repair proteins directly activates neuronal apoptotic pathways (Lovell et al., 2011) with impaired BER function playing a critical pathogenic role (Weissman et al., 2009; Weissman et al., 2007). AD brain tissues exhibit not only accumulation of oxidized bases but also significantly reduced expression and activity of BER proteins including DNA polymerase β (Pol β), uracil-DNA glycosylase (UDG), and 8-oxoG DNA glycosylase (OGG1) (Canugovi et al., 2013; Iida et al., 2002; Lovell et al., 2000). These findings may help elucidate the missing link between oxidative stress and neuronal death.

Despite the pivotal role of DNA glycosylases in AD, these repair initiators have received considerably less research attention compared to downstream BER enzymes such as APE1 and DNA polymerases, and specific modulators remain limited(Hans et al., 2020). Currently available FDA-approved drugs (acetylcholinesterase inhibitors and NMDA receptor antagonists) only alleviate symptoms without halting underlying pathology (Lantyer et al., 2021). As the first line of defense against oxidative base lesions, the BER pathway and its initiating glycosylases are emerging as critical nodes interfacing with classic AD pathologies (Raper et al., 2021). Therefore, targeting DNA glycosylases to restore BER function represents a promising and unmet therapeutic strategy for AD. This review aims to fill this gap by systematically elucidating the roles of DNA glycosylases in AD pathogenesis and exploring their therapeutic potential.

2. Oxidative damage and the BER pathway in AD

2.1. Oxidative DNA damage: an early trigger of AD pathogenesis

Oxidative DNA damage is not a secondary consequence but an early driver of AD(Zuo, 2025). In the preclinical stage of AD, elevated levels of oxidative damage markers (8-oxoG, 8-OHdG, γH2AX) are detected in the frontal lobe and hippocampus-brain regions critical for memory-concurrently with glial cell activation(Bradley-Whitman et al., 2014; Mizuno et al., 2022). Mitochondrial DNA (mtDNA) is particularly susceptible to oxidative damage due to lack of histone protection and proximity to the electron transport chain, harboring 3–5 times more 8-oxoG lesions than nuclear DNA and creating a self-amplifying cycle of oxidative stress(Gabbita et al., 1998; Lovell and Markesbery, 2007). Body fluid studies report increased oxidized purine nucleosides (e.g., 8 oxoG/8 OHdG) and reduced repair products in AD, consistent with impaired BER capacity(Lovell et al., 1999; Sliwinska et al., 2016). This imbalance reflects failure of BER to keep pace with DNA damage, leading to conversion of single-strand breaks (SSBs) into toxic double-strand breaks (DSBs) and neuronal senescence (Lovell et al., 1999; Sedelnikova et al., 2004). Notably, oxidative damage interacts synergistically with core AD pathologies: oxidatively modified Aβ42, upon binding Cu^{2+}, catalyzes Fenton reactions generating hydroxyl radicals(Su et al., 2020), while hyperphosphorylated tau suppresses expression of key BER enzymes including OGG1 and AP endonuclease 1 (APE1). Consequently, oxidized bases accumulate in genomic regions associated with synaptic plasticity, impairing the transcription of immediate early genes (IEGs) and providing a mechanistic explanation for early memory decline (Kirova et al., 2015; Shanbhag et al., 2019). Thus, oxidative damage in the AD brain serves as both an initial insult and a critical nexus linking Aβ accumulation, tau pathology, bioenergetic deficits, and neuronal loss.

2.2. The BER pathway: mechanisms and dysregulation in AD

The BER pathway is a conserved, multi-step process responsible for repairing oxidized, alkylated, or deaminated base lesions (Caldecott, 2022; Lee and Kang, 2019; Madabhushi et al., 2014), with three core stages: recognition/excision, AP site processing, and repair synthesis/ligation (Fig. 1). BER is initiated by specific monofunctional or bifunctional DNA glycosylases. Monofunctional glycosylases (e.g., UDG, MPG) possess glycosylase activity but lack an associated AP lyase activity(Hua and Sweasy, 2024). Bifunctional glycosylases (e.g., OGG1, NEIL1) exhibit both glycosylase and AP lyase activities(Bakman et al., 2023). First, DNA glycosylases recognise damaged bases on the DNA strand by catalysing hydrolysis of the N-glycosidic bond, causing the damaged base to protrude from the double helix and be excised (Dizdaroglu, 2005; Huffman et al., 2005; Stivers and Jiang, 2003), generating an AP site with an intact DNA phosphodiester backbone (Krokan et al., 2002; Mullins et al., 2019); Subsequently, the AP site is processed. In the case of monofunctional glycosylases, APE1 cleaves the phosphodiester backbone 5′ to the AP site, generating a single-strand break with 3′-hydroxyl (3′-OH) and 5′-deoxyribose phosphate (5′-dRP) termini(Demple and Sung, 2005; Robson and Hickson, 1991). If a bifunctional glycosylase is involved, it may directly cleave the AP site via β- or β/δ-elimination, producing a strand break with a 3′-phosphorylated α,β-unsaturated aldehyde (3′-PUA) or 3′-phosphate (3′-P) group(Prakash et al., 2012). The resulting termini are then prepared for repair. Pol β removes the 5′-dRP group via its dRP lyase activity, while APE1 can process the 3′-PUA or 3′-P residues through its phosphodiesterase activity. Finally, depending on the nature of the 5′-dRP group, repair proceeds via either the short-patch or long-patch BER sub-pathway(Horton et al., 2000). Short-patch BER involves the insertion of a single nucleotide by Pol β, followed by ligation facilitated by the XRCC1-Ligase III complex (Wilson et al., 2007). In contrast, long-patch BER recruits DNA polymerases β/δ, PCNA, FEN1, and DNA Ligase I to perform strand-displacement synthesis of 2–13 nucleotides (Fan and Wilson, 2005; Levin et al., 2004; Wu et al., 1996). This coordinated process ultimately restores DNA integrity and safeguards genomic stability (Frosina et al., 1996). In AD brains, BER dysfunction is characterized by reduced expression/activity of key enzymes (OGG1, Pol β) and accumulation of repair intermediates, exacerbating genomic instability and neuronal death.

3. Overview of DNA glycosylases

3.1. Classification and structural characteristics

DNA glycosylases are the rate-limiting initiators of the BER pathway, and their activity directly determines repair efficiency. Mammalian DNA glycosylases are classified into four structural superfamilies based on conserved domains (Fig. 2): Uracil-DNA glycosylases (UDGs): Specialize in excising uracil from DNA, preventing G:C→A:T transitions caused by cytosine deamination or dUTP misincorporation. Key members include UNG and SMUG1. Helix-hairpin-helix (HhH) glycosylases: The primary family responsible for repairing oxidative damage, including OGG1 (8-oxoG repair) and MUTYH (A:8-oxoG mismatch repair). They share a conserved HhH motif and a [4Fe-4S] cluster for substrate binding. 3-Methylpurine DNA glycosylases (MPGs): Recognize a broad range of alkylated purines (e.g., 3-MeA, 7-MeG) and deaminated bases (e.g., hypoxanthine). Endonuclease VIII-like (NEIL) glycosylases: Specialize in repairing oxidized pyrimidines and formamidopyrimidines in single-stranded DNA (ssDNA) and transcription bubbles. The NEIL family includes NEIL1, NEIL2, and NEIL3, with distinct substrate preferences and tissue expression patterns(Jacobs and Schär, 2012). Despite their diverse catalytic domains, nearly all DNA glycosylases employ a conserved base-flipping mechanism: they extrude the damaged nucleotide from the DNA double helix into a specific binding pocket, enabling precise recognition and excision without disrupting the intact DNA

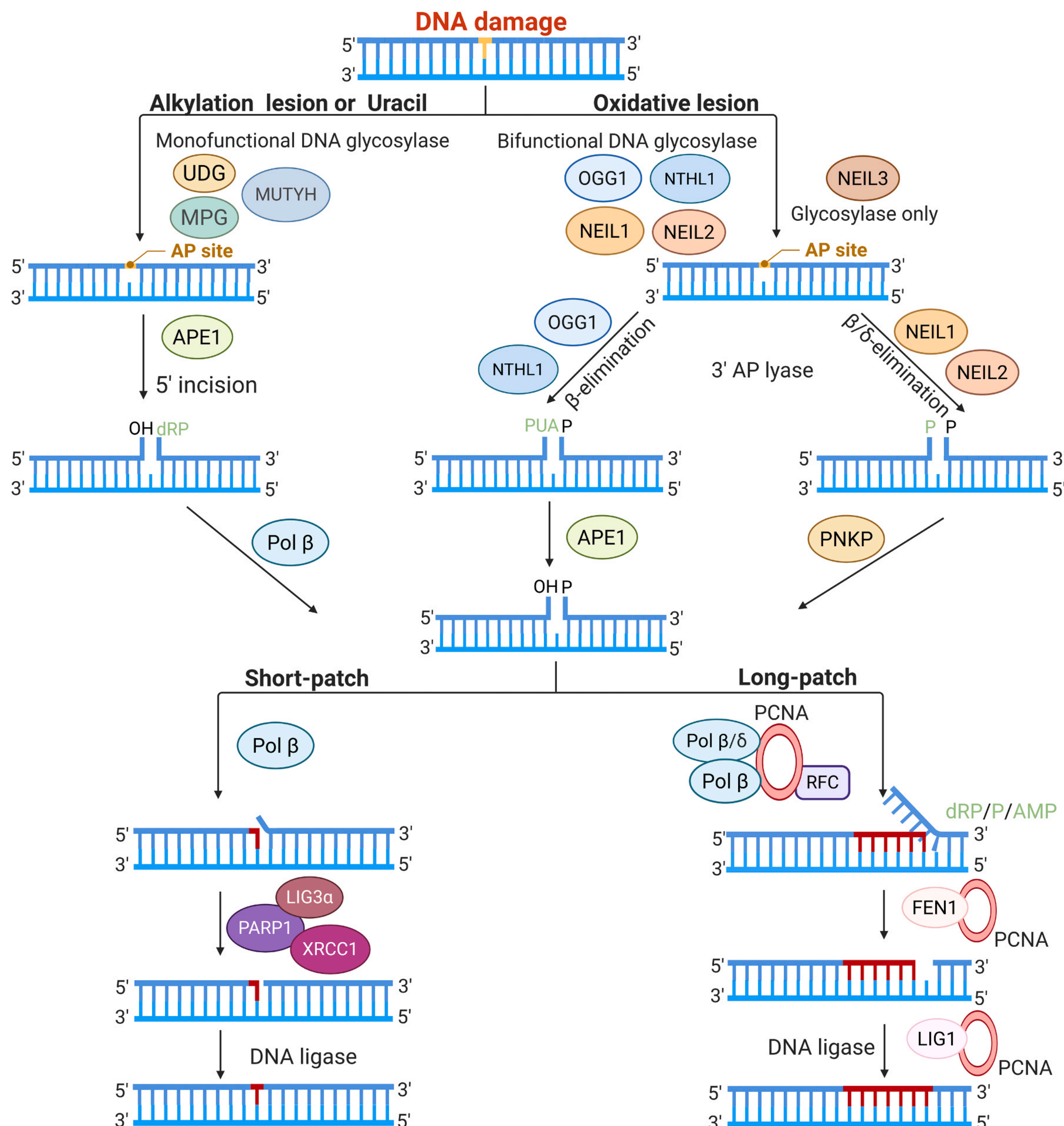

Fig. 1. Overview of the BER pathway. The BER pathway is initiated by DNA glycosylases that recognize and excise damaged bases, generating an abasic (AP) site. Subsequent steps involve AP site processing, gap filling, and ligation, proceeding through either short-patch or long-patch sub-pathways to restore genomic integrity.

structure(Brooks et al., 2013; Hitomi et al., 2007; Mullins et al., 2019; Stivers, 2004). Many eukaryotic glycosylases also contain non-catalytic domains that regulate subcellular localization (e.g., mitochondrial targeting sequences) and protein-protein interactions (PPIs)(Torgasheva et al., 2022).

3.2. Regulatory mechanisms of DNA glycosylase activity

The activity and abundance of DNA glycosylases are tightly regulated through multiple layers to ensure precise BER responses. Genetic and epigenetic regulation: Polymorphisms in glycosylase genes (e.g., OGG1 Ser326Cys) affect enzyme activity and AD susceptibility. Promoter methylation and histone modifications also modulate glycosylase expression in AD brains. Alternative splicing: Genes such as OGG1 and MUTYH generate multiple isoforms with distinct subcellular localizations (nuclear vs. mitochondrial) and functions (de Sousa et al., 2021; Schärer, 2001). Post-translational modifications (PTMs): Phosphorylation, acetylation, and glutathionylation dynamically regulate glycosylase stability, catalytic activity, and subcellular localization. For example, Aβ42-induced glutathionylation of OGG1 cysteine residues inhibits its 8-oxoG repair activity (Carter and Parsons, 2016). PPIs: Glycosylases interact with BER components (e.g., OGG1-APE1) and replication/transcription factors (e.g., MUTYH-PCNA) to coordinate repair processes.

An additional layer of regulatory complexity arises from substrate ambiguity. Chemical oxidation of 5-methylcytosine (5-mC) generates products structurally indistinguishable from those produced by TET-mediated active demethylation(Zhao et al., 2014). This overlap implicates DNA glycosylases in processing these modified bases, potentially linking BER to active DNA demethylation and gene expression control. Such substrate promiscuity suggests glycosylases function not only as genome guardians but also as epigenetic modulators - a duality particularly relevant to the transcriptional dysregulation observed in AD (Wang et al., 2025).(Table 1)

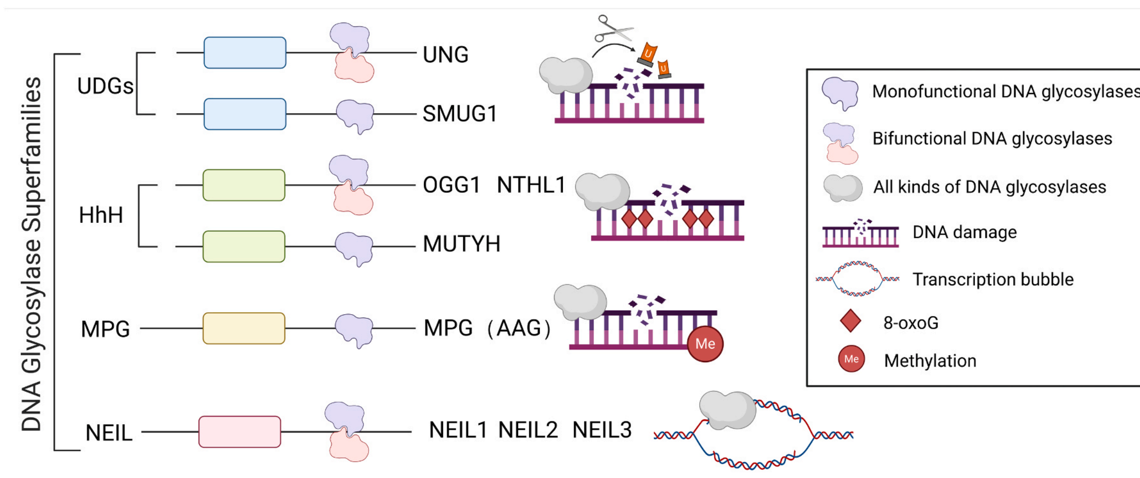

Fig. 2. Classification of DNA Glycosylase Superfamilies. Mammalian DNA glycosylases are categorized into four major superfamilies: UDGs, HhH glycosylases, MPGs, and NEIL glycosylases.

Table 1
DNA Glycosylases Associated with AD.

Superfamily	DNA glycosylase	Catalytic Type	Primary Substrates	Role in AD Pathogenesis
HhH	OGG1	Bifunctional	8-OxoG in dsDNA	Deficiency leads to 8-oxoG accumulation, PARP activation, neuroinflammation, and neuronal death
	MUTYH	Monofunctional	The base opposite 8-oxo-G/C/G in dsDNA	Aberrant upregulation promotes microglial activation and impairs hippocampal neurogenesis
MPGs	MPG	Monofunctional	3-MeA, 7-MeG, Hx, εA, HεA	Hyperactivity generates toxic AP sites, exacerbating DNA strand breaks and neuronal injury
NEIL	NEIL1	Bifunctional	Oxidized pyrimidines in ssDNA and dsDNA	Cu^{2+}/Fe^{3+} binding inhibits activity, leading to transcription-associated DNA damage
	NEIL2	Bifunctional	Similar to ssDNA in bubbles and loops	Inhibition by metal ions disrupts TCR, impairing synaptic gene expression
	NEIL3	Bifunctional	Oxidized pyrimidine in ssDNA, G-quadruplexes	Supports hippocampal neurogenesis; deficiency exacerbates Aβ pathology

4. Key DNA glycosylases: from molecular mechanisms to therapeutic targeting

The BER pathway is functionally compromised in AD, with dysfunction of key DNA glycosylases playing a central role in pathological progression. summarizes the characteristics of AD-associated DNA glycosylases, and Table 2 recapitulates the mechanisms of action and therapeutic potential of agonists or inhibitors targeting these enzymes. This section focuses on the molecular mechanisms and therapeutic potential of the most extensively studied glycosylases: OGG1, MUTYH, MPG, and the NEIL family.

4.1. OGG1

4.1.1. Molecular characteristics

The human OGG1 gene is located on chromosome 3p25–26 and

Table 2
DNA Glycosylase-Targeted Modulators.

Target	Strategy	Agent	Mechanism	Efficacy	Limitations
OGG1	Agonist	TH10785	Stabilizes active site, enhances 8-oxoG excision (>10 ×); bypasses APE1-dependent BER	↑ 8-oxoG clearance, ↓ tau phosphorylation	Pro-inflammatory risk, BBB penetration needed
	Inhibitor	TH5487	Blocks 8-oxoG binding, suppresses NF-κB-driven transcription	↓ Neutrophil infiltration, anti-inflammatory	DNA-damage accumulation in chronic use
	Inhibitor	Hydrazide-based compounds	Blocks Schiff base formation during catalysis	Enhanced inhibitor properties, valuable	No specific BBB-penetrant ; Potential in AD unexplored
	Inhibitor	Tetrahydroquinoline sulfonamide derivatives	Improved potency and selectivity for OGG1 inhibition	chemical tools for probing OGG1 function	Potential in AD unexplored
MUTYH	Inhibitor	Genetic KO / emerging compounds	Reduces A:8-oxoG excision, PARP1 hyperactivation, DAM polarization	Memory rescue, ↓ microgliosis, ↑ neurogenesis	No specific BBB-penetrant inhibitors
MPG	Inhibitor	Quercetin	Inhibits MPG, reduces Aβ/tau pathology	Delays AD-like pathology	Complex polypharmacology
NEIL1	Agonist	Purine analog screen compounds	First small-molecule inhibitors of NEIL1 identified through high-throughput screening	Proof-of-concept for pharmacological NEIL1 modulation	Potential in AD unexplored
NEIL2	Reactivation	Clioquinol + metal chelators	Chelates Cu^{2+}/Fe^{3+}, restores transcription-coupled repair	Restores repair, ↓ transcription damage	Requires combination, off-target risk
NEIL3	Enhancement	Overexpression / modulation	Repairs G-quadruplex/telomeric lesions, supports DSB repair	Supports neurogenesis, ↓ γ-H2AX/Aβ co-localization	No specific drugs, mechanism unclear

encodes multiple isoforms via alternative splicing. The two major isoforms are α-OGG1 (345 amino acids, nuclear localization) and β-OGG1 (424 amino acids, mitochondrial localization) (Nishioka et al., 1999; Takao et al., 1998). Both isoforms share the first 315 amino acids containing the HhH-K/GPD catalytic domain, but α-OGG1 contains a nuclear localization signal (NLS) that prevents mitochondrial entry (Hashiguchi et al., 2004). Notably, β-OGG1 lacks 8-oxoG repair activity, and α-OGG1 is the key isoform responsible for repairing both nuclear and mtDNA damage in neurons (Arai et al., 2006b; Audebert et al., 2002).

OGG1 is a bifunctional glycosylase with glycosylase and AP lyase activity. Its primary biological function is to recognize and excise 8-oxoG from double-stranded DNA (dsDNA), restoring G:C base pairs and preventing G:C→T:A transversion mutations(Thayer et al., 1995). Beyond 8-oxoG, OGG1 also excises other oxidatively induced lesions, including 2,6-diamino-4-hydroxy-5-formamidopyrimidine (FapyG), a prevalent formamidopyrimidine lesion generated by oxidative stress(Hu et al., 2005). Studies in OGG1-deficient mice have demonstrated that OGG1 is the primary glycosylase responsible for FapyG repair in both nuclear and mitochondrial DNA, as evidenced by significant accumulation of this lesion and loss of repair capacity in the absence of OGG1 (Hu et al., 2005). OGG1 is ubiquitously expressed, with high levels in tissues with high metabolic activity (e.g., brain, testis), underscoring its critical role in maintaining genomic stability (Nishimura, 2001; Shinmura et al., 1997).

4.1.2. Pathogenic mechanisms of OGG1 in AD

OGG1-mediated 8-oxoG repair is systemically dysregulated in AD, representing an early and sustained pathological event (Fig. 3)(Lovell et al., 2011). Post-mortem studies show that OGG1 activity is decreased in MCI brains and further declines in late-stage AD, accompanied by loss-of-function mutations (e.g., Ser326Cys). This impairment correlates with increased 8-oxoG levels, Aβ plaque deposition, tau hyperphosphorylation, and neuronal loss(Shao et al., 2008). Three primary mechanisms underlie OGG1 dysfunction: (1) Subcellular mislocalization: under oxidative stress conditions, OGG1 can be mislocalized to the cytoplasm and mitochondrial cristae, which may limit its access to nuclear and mtDNA (Oka et al., 2021). While hyperphosphorylated tau has been associated with this mislocalization, a direct tau-dependent sequestration mechanism remains to be established; (2) Covalent modification by oxidative stress: OGG1 is redox sensitive; S glutathionylation and other thiol modifications can inhibit its catalytic function under oxidative stress. Aβ42 oligomer-induced neuronal oxidative stress may elevate the GSSG/GSH ratio, leading to the glutathionylation and subsequent inactivation of OGG1(Gupta et al., 2021). (3) Induction of neuroinflammation and apoptosis: OGG1 deficiency leads to 8-oxoG accumulation, which activates PARP1. Excessive PARP1 activation depletes NAD^+ and ATP, triggering AIF-mediated caspase-independent apoptosis.This PARP-NAD^+ axis represents a common pathological mechanism across neurodegenerative disorders(Hu et al., 2026): PARP1 hyperactivation in response to persistent DNA damage not only disrupts energy metabolism and mitochondrial function but also inhibits sirtuin activity, compromising cellular antioxidant and anti-inflammatory capacity, ultimately culminating in parthanatos - a caspase-independent programmed cell death. Beyond neuronal death, PARP1 activation also promotes NF-κB binding to inflammatory gene promoters, inducing microglial activation and release of pro-inflammatory cytokines (TNF-α, IL-1β)(Mangerich and Bürkle, 2012). This multi-layered dysregulation positions OGG1 as a critical node linking oxidative stress to neuroinflammation.

4.1.3. TherapeutiC Targeting of OGG1: agonist and inhibitor strategies

The concept of pharmacologically targeting OGG1 for therapeutic benefit was first established by pioneering work from Baptiste and colleagues, who demonstrated the feasibility of small-molecule modulation of OGG1 activity(Baptiste et al., 2018). Concurrently, the first potent and selective OGG1 inhibitors were identified through high-throughput screening, yielding hydrazide-based molecules (IC_{50} <1 μM) that specifically block Schiff base formation during catalysis (Donley et al., 2015). Subsequent work from the Kool laboratory developed additional inhibitors with improved potency and selectivity, providing valuable chemical tools for probing OGG1 function(Kant et al., 2021; Tahara

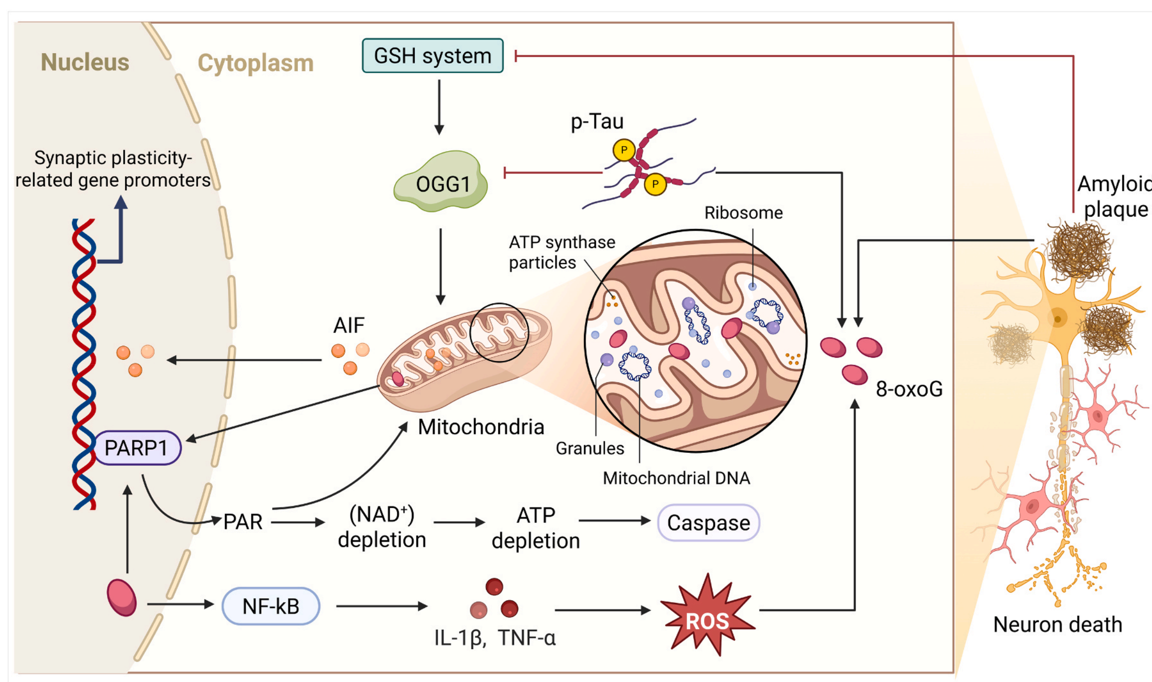

Fig. 3. The role of OGG1 in AD pathogenesis. In early stage of AD, reduced OGG1 function results in 8-oxoG accumulation, initiating DNA damage signaling. The resulting 8-oxoG promotes neuroinflammation via PARP overactivation and glial responses, induces nuclear genotoxic stress, and causes epigenetic dysregulation that sustains inflammation. Concurrently, OGG1 is directly compromised by AD hallmarks ultimately culminating in neuronal death.

et al., 2018; Tahara et al., 2019). Building on these foundations, the Helleday consortium characterized TH5487, an OGG1 inhibitor with anti-inflammatory activity in cellular and *in vivo* models (Hanna et al., 2020; Michel et al., 2022), while Michel et al. identified TH10785 as an OGG1 agonist that enhances 8-oxoG excision and introduces non-native β,δ-lyase activity (Michel et al., 2022).

Agonists for early-stage AD: TH10785 enhances 8-oxoG excision (>10-fold) and confers non-native β,δ-lyase activity, enabling direct cleavage of AP sites and bypassing APE1-dependent BER(Geng et al., 2025; Hank et al., 2026). In cellular models, reduced 8-oxoG attenuates tau phosphorylation and improves synaptic function; however, *in vivo* cognitive effects in AD models remain to be demonstrated (Michel et al., 2022; Oka et al., 2021; Pao et al., 2020).

Inhibitors for late-stage AD: persistent 8-oxoG accumulation drives chronic neuroinflammation via NF-κB activation. TH5487 reduces NF-κB binding to inflammatory gene promoters, dampens cytokine release, and inhibits neutrophil infiltration *in vivo* (Hanna et al., 2020). it has been hypothesized that backup repair by NEIL1/2 may prevent catastrophic genomic damage upon OGG1 inhibition, though direct evidence for this compensatory mechanism *in vivo* remains to be established. Beyond AD, TH5487 has shown efficacy in suppressing cancer cell growth, inhibiting fibrosis, and sensitizing tumors to ionizing radiation(Jaruga et al., 2025), highlighting the broad therapeutic potential of OGG1 modulation.

4.2. MUTYH

4.2.1. Molecular characteristics

The human MUTYH gene is located on chromosome 1p34.3 and generates multiple isoforms via alternative splicing of three distinct promoters. The major isoforms are localized to the nucleus (β3, β5, γ3) and mitochondria (α3), enabling repair of both nuclear and mtDNA damage in the hippocampus(Boldogh et al., 2001; Oka and Nakabeppu, 2011). Functioning within the BER pathway, MUTYH is localized to both mitochondrial and nuclear DNA in the human hippocampus(Al-Tassan et al., 2002). MUTYH is a monofunctional glycosylase that excises adenine mispaired with 8-oxoG, preventing G:C→T:A mutations. Its substrate recognition is mediated by a conserved HhH motif and a [4Fe-4S] cluster, which detects the unique 2-amino group of 8-oxoG in the DNA major groove (Conlon et al., 2024; Trasviña-Arenas et al., 2025). MUTYH interacts with the replication factor PCNA to recruit replication machinery and enhance repair efficiency at replication forks (Englander et al., 2002; Parker and Eshleman, 2003; Tao et al., 2004).

4.2.2. Pathogenic mechanisms of MUTYH in AD

MUTYH exhibits a tissue-specific expression pattern in AD: it is downregulated in peripheral blood lymphocytes but upregulated in hippocampal and cortical microglia, correlating with 8-oxoG burden (Abentung et al., 2025; Mizuno et al., 2021). This transforms MUTYH from a "repair enzyme" to a "damage amplifier" through three mechanisms (Fig. 4): (1) inducing neuronal apoptosis: Aβ42-triggered ROS elevates mtDNA 8-oxoG: A mismatches; MUTYH-initiated adenine excision generates SSBs that persist due to saturation of downstream Pol β/XRCC1 capacity, activating PARP1, depleting NAD⁺/ATP, and triggering AIF-mediated apoptosis(Sheng et al., 2012); (2) Enhancing neuroinflammation: MUTYH-overexpressing microglia polarize toward a pro-inflammatory disease-associated microglia (DAM) phenotype, secreting TNF-α and IL-1β, which impairs hippocampal neurogenesis and memory encoding(Mizuno et al., 2021); (3) Interacting with p53 pathway:in sporadic AD, upregulated p53 enhances MUTYH transcription while impairment of p53-mediated caspase-3 activation shifts neuronal death toward PARP-AIF-dependent necrosis (Hooper et al., 2007; Johnson et al., 1999; Poot, 2025). These insights provide a theoretical foundation for early therapeutic interventions aimed at either inhibiting MUTYH or precisely regulating its BER activity to break this pathogenic cycle.

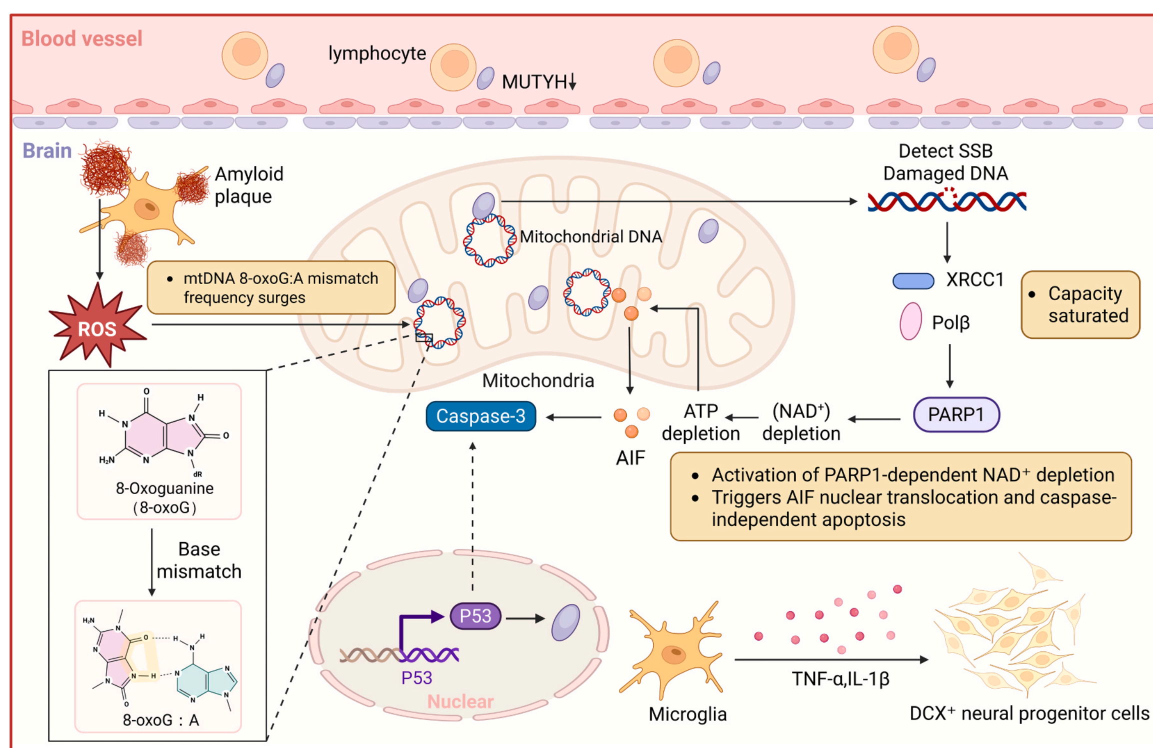

Fig. 4. The role of MUTYH in AD pathogenesis. MUTYH expression is downregulated in peripheral lymphocytes but upregulated in the brain. In neurons, Aβ stress leads to MUTYH-initiated repair that, via downstream saturation, causes persistent DNA breaks, pathological PARP1 activation, and energy depletion, culminating in AIF-mediated apoptosis. p53 upregulation enhances this cycle, favoring neuronal death. In glia, MUTYH overexpression promotes a pro-inflammatory phenotype, synergistically contributing to neurodegeneration.

4.2.3. Therapeutic Potential of MUTYH

Although specific MUTYH inhibitors for AD have not yet entered clinical trials, gene knockout studies have clearly demonstrated that inhibiting MUTYH activity significantly ameliorates AD-related pathologies and cognitive deficits. Study indicates that the accumulation of the oxidatively damaged base 8-oxoG in the brains of AD patients is a key factor triggering neurodegeneration. MUTYH exacerbates this process by promoting microglial activation and impairing hippocampal neurogenesis, thereby contributing to memory impairment in AD mouse models. Specifically, MUTYH gene knockout effectively improves memory function, significantly reduces microglial activation, and alleviates impairments in hippocampal neurogenesis in these mice(Mizuno et al., 2021). Collectively, these findings support MUTYH inhibition as a promising strategy for AD treatment, particularly in patients with high microglial activation.

4.3. MPG

4.3.1. Molecular characteristics

The human MPG gene (also known as AAG) is located on chromosome 16p13.3 and encodes a 298-amino acid protein with a broad substrate specificity for alkylated and deaminated purines(Izumi et al., 1997; Vickers et al., 1993). MPG uses a hydrophobic "base-insertion" loop to flip damaged bases into its active site, where Asp238 catalyzes N-glycosidic bond cleavage(Lau et al., 1998). MPG exhibits the broadest substrate specificity among mammalian DNA glycosylases, recognizing and excising a wide array of alkylated and deaminated purines. Its substrates include 3-methyladenine (3-MeA), 7-methylguanine (7-MeG), hypoxanthine (Hx), and lipid peroxidation-derived adducts such as 1,N6-ethenoadenine (εA)(Lee et al., 2009; Wang et al., 2006). Unlike other glycosylases, MPG's base excision rate is slower than adduct formation, leading to transient accumulation of AP sites- a key determinant of cellular fate(Maher et al., 2007). Genetic studies in MPG-knockout mice have confirmed its specific role in clearing εA and Hx adducts, while the repair of oxidative lesions like 8-oxoG remains intact, clearly delineating the pathways for alkylation versus oxidative damage repair (Hang et al., 1997). MPG is recruited to active genes by the transcription elongation complex, preferentially repairing alkylation damage on the transcribed strand via transcription-coupled repair (TCR) (Montaldo et al., 2019).

4.3.2. Pathogenic mechanisms of MPG in AD

MPG plays a dual role in neuronal function, depending on the pathological context (Fig. 5). Under physiological conditions, AP sites generated by MPG act as epigenetic signaling nodes: APE1 processes these sites and recruits histone-modifying complexes (e.g., HDAC1), altering chromatin architecture to fine-tune expression of genes associated with neurodevelopment and synaptic plasticity. MPG knockout mice display reduced anxiety-like behaviors and enhanced memory, confirming MPG-mediated epigenetic modulation shapes cognitive function (Bordin et al., 2024). In contrast, under chronic oxidative stress characteristic of AD, MPG hyperactivity generates excessive AP sites that overwhelm downstream BER capacity. These accumulated AP sites are converted into toxic SSBs and DSBs, triggering neuronal death- a pathological cascade mirroring MPG's detrimental role in ischemia- reperfusion injury (Ebrahimkhani et al., 2014). Thus, subtle fluctuations in MPG activity may drive AD progression via dual mechanisms: epigenetic modulation of synaptic gene networks and, under severe oxidative stress, catastrophic AP site accumulation accelerating neuronal death.

4.3.3. Therapeutic potential of MPG

Although specific MPG inhibitors with validated *in vivo* efficacy in AD models remain under development, natural compounds with pleiotropic neuroprotective effects have been shown to mitigate MPG-mediated pathology indirectly. Quercetin, a widely distributed flavonoid with well-documented anti-inflammatory and neuroprotective

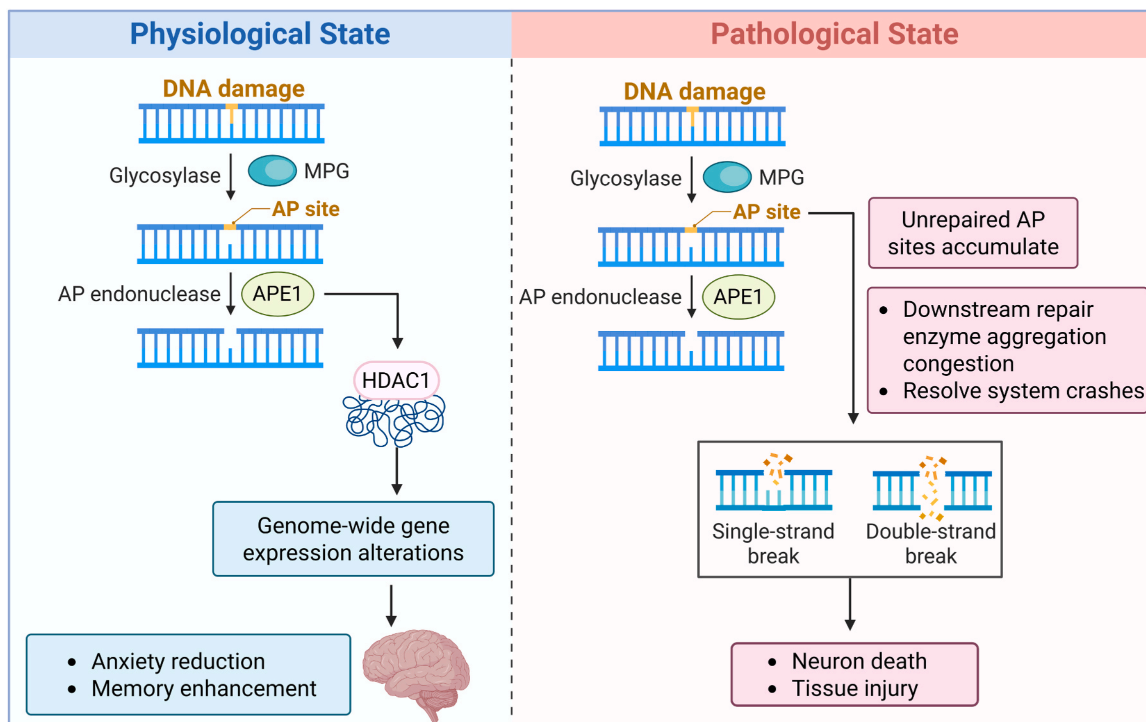

Fig. 5. The dual role of MPG in neuronal regulation and pathology. Under physiological conditions during development, the AP sites generated by MPG activity function as epigenetic signaling nodes. These sites are processed by APE1, which recruits histone-modifying factors to remodel chromatin states. This epigenetic regulation subsequently modulates gene networks involved in neural development and synaptic plasticity, thereby influencing behaviors such as anxiety and memory formation. In contrast, under pathological conditions like ischemia-reperfusion, MPG hyperactivity leads to excessive generation of AP sites that surpass the capacity of the downstream repair machinery.

properties, has been shown to ameliorate core AD pathologies including Aβ aggregation and tau hyperphosphorylation, primarily by modulating pro-inflammatory cytokine secretion and attenuating the chronic neuroinflammatory microenvironment characteristic of AD(Zhang and Yan, 2023). While quercetin's neuroprotective effects in AD are well-established, direct evidence for its specific inhibition of MPG catalytic activity (with defined kinetics) is currently lacking. Instead, quercetin likely exerts its beneficial effects through multiple mechanisms, including antioxidant activity, anti-inflammatory signaling, and modulation of multiple enzyme systems, which collectively may reduce the oxidative stress burden that drives MPG hyperactivation in AD. This finding suggest that while direct MPG inhibitors remain a promising therapeutic concept, current evidence supports a multi-faceted approach combining targeted MPG modulation with broader anti-inflammatory and antioxidant strategies for AD intervention.

4.4. NEIL family

4.4.1. Molecular characteristics

The NEIL family (NEIL1, NEIL2, and NEIL3) belongs to the Fpg/Nei superfamily and specializes in repairing oxidized pyrimidines and formamidopyrimidines. These enzymes are dedicated to recognizing and excising a variety of base lesions induced by ROS, exogenous chemicals, and metabolic byproducts, thereby safeguarding genomic integrity by preventing replication errors, DNA breaks, and mutagenesis(Hazra et al., 2002a; Hazra et al., 2002b). Structurally, NEIL proteins share a dual-domain architecture: an N-terminal region containing the H2TH motif for DNA binding and the catalytic active site, and a C-terminal domain that contributes to substrate specificity(Aliyaskarova, 2022). The catalytic activity of NEIL1 resides in its N-terminal domain, with Pro2 and Glu3 constituting the key active-site residues essential for catalysis(McCullough et al., 2025). NEIL2 harbors an additional C-terminal zinc finger motif homologous to that of bacterial Fpg, while NEIL3 possesses a significantly extended C-terminus with both classical and RanBP-type zinc finger domains, which are postulated to mediate interactions with ssDNA and chromatin remodeling complexes (Hwang et al., 2025a).

Beyond structural divergence, the NEIL family exhibits pronounced functional specialization characterized by distinct substrate preferences and tightly regulated spatiotemporal expression patterns throughout the cell cycle. NEIL1 is active on both ssDNA and double-stranded DNA (dsDNA) substrates and can process guanidine-derived lesions (Gh, Sp) (Dou et al., 2003; Zhao et al., 2010), whereas NEIL2 displays a strong preference for ssDNA and transcription bubble structures, reflecting its specialized role in TCR. NEIL3, by contrast, recognizes the broadest spectrum of lesions, including FapyG, FapyA, thymidine glycol (Tg), and other oxidized bases, with a marked affinity for ssDNA, G-quadruplex structures, and specific genomic regions such as telomeres and interstrand cross-links (ICLs)(Chen et al., 2022). Unrepaired lesions of these types can lead to replication fork stalling, base misincorporation, and subsequent genomic instability, which are closely linked to carcinogenesis and neurodegeneration(Zhou and Parsons, 2020).

Functionally, NEIL family members exhibit precise spatiotemporal complementarity to ensure comprehensive DNA damage repair. NEIL1 expression peaks during the S phase of the cell cycle, where it interacts directly with replication proteins (PCNA, FEN-1, RPA) to ensure timely repair of oxidative damage at the replication fork (Hegde et al., 2013; Rangaswamy et al., 2017). NEIL2 is specialized for TCR, collaborating with RNA polymerase II and associated factors to remove oxidized bases from actively transcribed genes, thereby minimizing transcription-associated mutagenesis(Banerjee et al., 2011; Mullins et al., 2019). Research on NEIL3 remains relatively scarce, though existing evidence indicates it not only recognises FapyG, FapyA, and Tg (Liu et al., 2010), but also exhibits differential binding to single- and double-stranded DNA. Its peak expression during G2 phase suggests it may continue surveying and repairing residual damage in post-replication stages(Hegde et al., 2013; Liu et al., 2012).

Evolutionary analyses across 157 vertebrate species reveal that the NEIL family has undergone adaptive evolution. Positive selection has acted on approximately 2.7% of codons, predominantly within the H2TH and zinc finger domains. This suggests that fine-tuning of DNA-binding affinity, enzymatic activity, and PPIs has been critical for adapting to varying oxidative stress levels across different lineages (Ahmad et al., 2022).

4.4.2. Pathogenic mechanisms of NEIL in AD

Transition metal ion dyshomeostasis (Cu^{2+}, Fe^{3+}, Zn^{2+}) is a hallmark of AD and directly impairs NEIL family function(Jagannatha et al., 1999). The accumulated metal ions inhibit NEIL-mediated repair of oxidized DNA damage and promote neurodegeneration (Hegde et al., 2009; Hegde et al., 2010). Specifically, elevated concentrations of Cu^{2+} and Fe^{3+} occupy the catalytic zinc finger domains of NEIL1 and NEIL2, blocking the β-elimination step during base excision. This leads to repair intermediate stalling, persistent oxidative base lesions, excessive PARP activation, and ultimately neuronal apoptosis. NEIL3 plays a distinct role in hippocampal dentate gyrus neural stem cells, where it rapidly repairs oxidative damage to maintain genomic integrity in progenitor cells, thereby supporting adult neurogenesis(Regnell et al., 2012). In AD mouse models, NEIL3 deficiency exacerbates Aβ plaque deposition, impairs adult hippocampal neurogenesis, and accelerates cognitive decline in a sex- and age-dependent manner(Egiazarian et al., 2022). NEIL3 also contributes to DNA double-strand break repair via the FA/BRCA pathway; when NEIL3 function is impaired -whether by metal chelation or transcriptional downregulation-DSB repair is delayed, γ-H2AX foci co-localize with Aβ plaques, and neuronal death accelerates (Li et al., 2020; Li et al., 2022). When NEIL3 function is impaired—-whether by metal chelation or transcriptional downregulation-DSB repair is delayed, γ-H2AX foci co-localize with Aβ plaques, and neuronal death accelerates (Fig. 6). These insights provide a theoretical foundation for future therapeutic strategies combining metal chelation with targeted NEIL pathway modulation.

4.4.3. Therapeutic targeting of NEIL

The NEIL glycosylase family (NEIL1, NEIL2, and NEIL3) represents a promising yet substantially underexplored therapeutic target for AD, with preclinical evidence highlighting its potential to modulate core pathological cascades including oxidative DNA damage accumulation, neuroinflammation, and impaired neurogenesis. Early proof-of-concept for pharmacological targeting of this family came from Jacobs and colleagues, who identified the first small-molecule inhibitors of NEIL1 through high-throughput screening(Jacobs et al., 2013). Their work demonstrated the feasibility of directly modulating NEIL1 activity with synthetic compounds, providing foundational chemical tools for probing NEIL1 function. Subsequent studies have further characterized the specificity and mechanism of these inhibitors, though their therapeutic potential in neurodegenerative contexts remains unexplored. In the case of NEIL3, genetic studies have provided compelling insights: NEIL3 knockout in AD mice exacerbates Aβ plaque deposition, impairs adult hippocampal neurogenesis, and accelerates cognitive decline, suggesting that targeted activation of NEIL3 may restore genomic stability in neural stem cells, alleviate Aβ-related pathology, and preserve cognitive function in late-stage AD(Hwang et al., 2025b). Additionally, metal chelation therapy represents a viable strategy to rescue NEIL1 and NEIL2 function in the AD brain: chelators such as clioquinol selectively reduce the accumulation of redox-active metal ions (Cu^{2+}/Fe^{3+}), which otherwise bind to the catalytic zinc finger domains of NEIL1 and NEIL2 to suppress their β-elimination activity; by relieving this metal-mediated inhibition, chelation therapy enhances the overall efficiency of the BER pathway, thereby reducing the burden of unrepaired oxidative DNA damage and ameliorating neuronal dysfunction in AD.

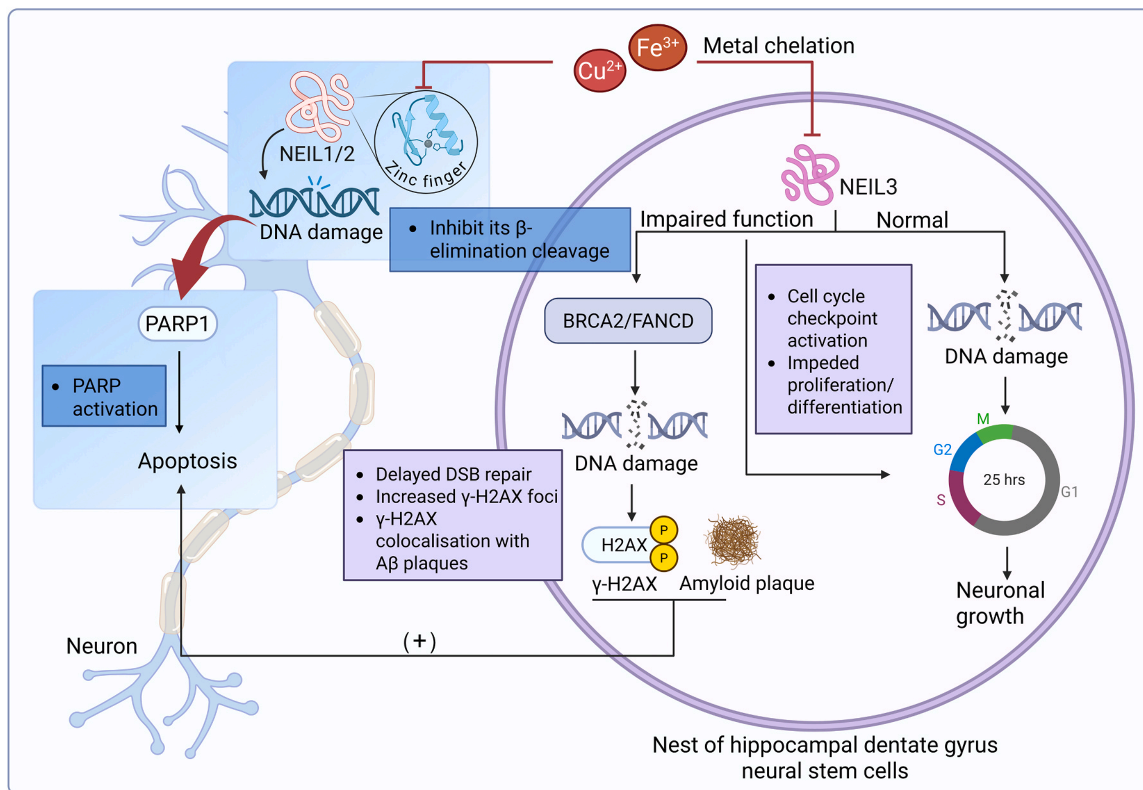

Fig. 6. Functional inhibition mechanisms of the NEIL family in AD. In the AD brain, accumulated Cu^{2+} and Fe^{3+} ions bind with high affinity to the catalytic zinc finger domains of NEIL1 and NEIL2, directly inhibiting their β-elimination activity. This results in stalled repair of oxidized bases, where functional suppression of NEIL1 induces replication stress, and inactivation of NEIL2 leads to the accumulation of transcription-associated DNA damage—collectively exacerbating genomic instability. Impaired NEIL3 function in hippocampal neural stem cells disrupts genomic integrity, activates cell cycle checkpoints, and significantly impedes adult neurogenesis. Concurrently, loss of NEIL3 weakens the repair of DNA double-strand breaks via the FA/BRCA pathway, increasing co-localization of γ-H2AX foci with Aβ plaques. These multi-pathway deficiencies ultimately converge to accelerate neuronal death, further amplified by PARP hyperactivation.

5. The role of DNA glycosylases in other brain diseases

DNA glycosylase dysfunction is not unique to AD but represents a common pathological feature across neurodegenerative diseases, highlighting the conserved role of genomic maintenance in brain health. In Huntington's disease (HD), OGG1 polymorphisms modulate 8-oxoG repair efficiency and influence age of disease onset; insufficient OGG1 activity accelerates expansion of pathogenic CAG trinucleotide repeats and promotes selective striatal neuron death(Fukae et al., 2005; Taherzadeh-Fard et al., 2010). In amyotrophic lateral sclerosis (ALS), downregulation of mitochondrial DNA repair enzymes including NEIL1 occurs in spinal motor neurons of presymptomatic SOD1 transgenic mice, suggesting mitochondrial genomic instability is an early causal driver of motor neuron degeneration(Murakami et al., 2007). In PD, mitochondrial MUTYH expression is upregulated in the substantia nigra of patients, a response that likely serves as a compensatory mechanism to counteract the elevated mtDNA damage in dopaminergic neurons; however, sustained MUTYH hyperactivation paradoxically triggers apoptotic signaling cascades and exacerbates the loss of vulnerable nigrostriatal dopaminergic neurons. Moreover, NEIL1 deficiency further aggravates MPTP-induced PD-like pathology in animal models by impairing the repair of oxidative DNA lesions, which in turn amplifies oxidative stress and neuroinflammation in the nigrostriatal pathway (Arai et al., 2006a;Arai et al., 2006a; Cardozo-Pelaez et al., 2012; Chen et al., 2023; Xue et al., 2020). These findings highlight the conserved role of DNA glycosylases in neurodegeneration and support the translational potential of BER-targeted therapies across multiple diseases.

Beyond neurodegeneration, DNA glycosylase dysfunction has been implicated in psychiatric conditions. Reduced OGG1 expression in euthymic bipolar disorder patients correlates with elevated oxidatively-induced DNA lesions, suggesting impaired BER capacity contributes to bipolar disorder pathogenesis (Ceylan et al., 2018). The importance of FapyG lesions in neurological conditions is increasingly recognized, with studies demonstrating that OGG1-mediated repair of both 8-oxoG and FapyG is essential for maintaining genomic stability in post-mitotic neurons. This extends the relevance of oxidative DNA damage and repair deficiency beyond neurodegeneration to neuropsychiatric diseases.

6. Future perspectives and conclusions

Oxidative DNA damage is a critical nexus linking aging, Aβ/tau pathology, neuroinflammation, and neuronal death in AD. DNA glycosylases, as the initiators and rate-limiting steps of the BER pathway, play an indispensable role in maintaining neuronal genomic integrity. The evidence synthesized in this review indicates that dysfunction of key glycosylases (e.g., OGG1, MUTYH, NEIL family) constitutes the molecular basis for decreased BER efficiency, exacerbated genomic instability, and accelerated disease progression in AD.

Although BER is the primary pathway for repairing oxidative base lesions such as 8-oxoG, existing evidence suggests significant compensatory and synergistic mechanisms within the DNA repair network. For example, recruitment of Nucleotide excision repair (NER) factors such as DDB2 and CSB promotes chromatin remodeling, thereby indirectly creating an accessible repair environment for BER enzymes (e.g., OGG1) (Menoni et al., 2012; Parlanti et al., 2012). Notably, in actively transcribed gene regions, CSB also facilitates the recruitment of the BER scaffold protein XRCC1(Menoni et al., 2018). This non-canonical mode of action indicates that NER is not merely a simple backup pathway for BER, but rather a critical auxiliary and regulatory system. The

contribution of NER becomes even more pronounced when damage types are complex, such as in the presence of clustered lesions or 8-oxoG adjacent to AP sites(Menoni et al., 2018; Sassa and Odagiri, 2020). Therefore, future investigations into DNA repair deficits in AD must transcend a singular focus on the BER pathway and adopt a systems biology perspective to examine the compensatory capacity of pathways such as NER and their dynamic alterations across different disease stages.

Another layer of complexity worthy of in-depth exploration is the substrate promiscuity of DNA glycosylases and their potential role in epigenetic regulation. The chemical oxidation of 5-mC can yield products indistinguishable from those generated by TET enzyme-mediated active demethylation. This overlap between chemical and enzymatic products complicates the cellular distinction between "damage" and "signaling" and positions DNA glycosylases at the crossroads of DNA damage repair and epigenetic regulation. Certain glycosylases, such as members of the NEIL family, have been demonstrated to process oxidized derivatives of 5-mC(Zhao et al., 2014). This implies that in the AD brain, glycosylase dysfunction not only leads to the accumulation of genomic damage but may also directly interfere with active DNA demethylation, thereby causing aberrant expression of genes associated with neuronal plasticity. Consequently, glycosylases may serve as key molecular links connecting oxidative stress to epigenetic dysregulation, offering a novel perspective for understanding the complex pathological mechanisms of AD.

Based on these insights, precision therapeutic strategies targeting DNA glycosylases hold considerable promise, but clinical translation requires consideration of the following critical factors: (1) Stage-Specific and Cell Type-Specific Targeting Strategies: The function of glycosylases is highly context-dependent, mandating that intervention strategies align with disease stage. In early-stage AD, characterized by acutely elevated oxidative stress and a potentially compensable BER system, activating OGG1 (e.g., with TH10785) to enhance 8-oxoG clearance and block initial genomic damage accumulation represents a rational approach. Conversely, in late-stage AD dominated by chronic inflammation, 8-oxoG persisting in microglia may act as a damage-associated molecular pattern (DAMP), driving pro-inflammatory gene expression via NF-κB through the "non-canonical" functions of OGG1 (e.g., as a transcriptional co-activator). In this context, inhibiting OGG1 (e.g., with TH5487) can effectively suppress neuroinflammation, while genomic stability is potentially maintained by backup glycosylases such as NEIL1/2. Strategies targeting MUTYH and MPG are more focused on inhibiting their "damage-amplifying" effects in specific cell types, such as activated microglia or stressed neurons. (2) Under-Characterized Glycosylases: The roles of most mammalian DNA glycosylases, including SMUG1, NTHL1, and TDG, remain almost entirely unexplored in AD. Given their unique functions in processing deamination, alkylation, and oxidative damage, investigating their involvement in AD pathology, particularly in epigenetic dysregulation, is a critical direction for future research. (3) Development of Modulators with Brain Bioavailability: Most current glycosylase agonists/inhibitors were primarily developed as chemical probes and have not been optimized for blood-brain barrier (BBB) penetration. Enhancing their bioavailability in the central nervous system through novel drug delivery systems, such as nanoparticles or prodrug designs, is a prerequisite for clinical translation. (4) Combination Therapeutic Strategies: Modulation of a single repair pathway may be insufficient to counter the complex pathological network of AD. Combining glycosylase modulators with metal ion chelators (to restore NEIL1/2 activity), anti-inflammatory agents, or Aβ/tau-targeted drugs may yield synergistic benefits. Notably, given that PARP1 hyperactivation in response to DNA damage signals is a common pathway leading to neuronal energy depletion and cell death (parthanatos), combining PARP1 inhibitors or NAD^+ precursors could represent an ideal adjunctive strategy to enhance the efficacy of glycosylase-targeted therapies.

In conclusion, DNA glycosylases represent promising novel therapeutic targets for AD. A deeper understanding of their molecular mechanisms and the development of brain-penetrant, stage-specific modulators will pave the way for the next generation of disease-modifying AD therapies.

Abbreviations

AD	Alzheimer's disease
Aβ	β-Amyloid
APE1	AP endonuclease 1
ALS	Amyotrophic lateral sclerosis
BBB	blood-brain barrier
BER	Base excision repair
DAM	Disease-associated microglia
DAMP	damage-associated molecular pattern
dsDNA	double-stranded DNA
DSBs	Double-strand breaks
FapyA	4,6-Diamino-5-formamidopyrimidine
FapyG	2,6-Diamino-4-hydroxy-5-formamidopyrimidine
FEN1	Flap endonuclease 1
Gh	Guanidine-2,6-diimidazolium
HD	Huntington's disease
HDAC1	Histone deacetylase 1
HhH	Helix-hairpin-helix
Hx	Hypoxanthine
ICLs	Interstrand Cross-Links
IEG	Immediate early gene
MCI	Mild cognitive impairment
MPGs	3-methylpurine DNA glycosylases
MPTP	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
mtDNA	Mitochondrial DNA
MUTYH	MutY Homolog DNA Glycosylase
NDs	Neurological degenerative disorders
NEIL	Nucleic acid endonuclease VIII-like
NFTs	Neurofibrillary tangles
NLS	Nuclear localization signal
OGG1	8-oxoguanine DNA glycosylase
PCNA	Proliferating cell nuclear antigen
PD	Parkinson's disease
Pol β	DNA polymerase
PTMs	Post-translational modifications
PPIs	Protein-protein interactions
RPA	Replication protein A
ROS	Reactive oxygen species
SOD1	Superoxide Dismutase 1
SP	Spiroimidazolium
SPs	Senile plaques
SSBs	Single-strand breaks
ssDNA	single-stranded DNA
TCR	Transcription-coupled repair
UDGs	Uracil DNA glycosylases
3-MeA	3-methyladenine
3′-P	3′-phosphate
3′-PUA	3′-phosphorylated-α,β-unsaturated aldehyde
5′-dRP	5′-deoxyribosyl phosphate
5-hC	5-hydroxycytosine
5-mC	5-methylcytosine
7-MeG	7-methylguanine
8-oxoG	8-oxoguanine
γH2AX	Phosphorylated H2AX
εA	1,N6-ethenoadenine

Authors' contributions

G.L. contributed to the literature search and manuscript design. X.Z. and Y.L. participated in the drafting of the manuscript. X.Z. and G.L. revised the manuscript. X.X., Z.M., Q.Y., R.W., Y.R., and F.C. contributed to figure organization. J.W. and Y.H., contributed to format check.

Consent for publication

All the authors listed have approved the manuscript that is enclosed.

Declaration of Generative AI and AI-assisted technologies in the writing process

The authors did not use any generative AI or AI-assisted technologies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

This study was supported by the National Natural Science Foundation of China (21961142009 to G.L. and 82501725 to X.Z.), Hangzhou Natural Science Foundation (2024SZRYBH090002 to X.Z.) and Medical and health Science and Technology Project of Zhejiang Province (2025KY1032 to X.Z.). We would like to thank the support from the Scientific Research Center, Hangzhou Medical College.

References

2025, 20252025. 2025 Alzheimer's disease facts and figures. Alzheimer's & Dementia 21, e70235.

Abentung, A., Sakshaug, T., Dumaru, R., Liabakk, N.B., Yang, M., Wang, J., Bjørås, M., Scheffler, K., 2025. DNA glycosylases Ogg1 and Mutyh influence gene expression of PRC2 targets associated with cognition. Cell. Mol. life Sci. CMLS 82, 307.

Ahmad, H.I., Afzal, G., Sadia, S., Haider, G., Ahmed, S., Saeed, S., Chen, J., 2022. Structural and evolutionary adaptations of Nei-Like DNA glycosylases proteins involved in base excision repair of oxidative DNA damage in vertebrates. Oxid. Med. Cell Longev. 2022, 1144387.

Aliyaskarova, U., 2022. The role of NEIL3 DNA glycosylase in the resistance to cisplatin.

Al-Tassan, N., Chmiel, N.H., Maynard, J., Fleming, N., Livingston, A.L., Williams, G.T., Hodges, A.K., Davies, D.R., David, S.S., Sampson, J.R., Cheadle, J.P., 2002. Inherited variants of MYH associated with somatic G:C–>T:A mutations in colorectal tumors. Nat. Genet 30, 227–232.

Arai, T., Fukae, J., Hatano, T., Kubo, S., Ohtsubo, T., Nakabeppu, Y., Mori, H., Mizuno, Y., Hattori, N., 2006a. Up-regulation of hMUTYH, a DNA repair enzyme, in the mitochondria of substantia nigra in Parkinson's disease. Acta Neuropathol. 112, 139–145.

Arai, T., Kelly, V.P., Minowa, O., Noda, T., Nishimura, S., 2006b. The study using wild-type and Ogg1 knockout mice exposed to potassium bromate shows no tumor induction despite an extensive accumulation of 8-hydroxyguanine in kidney DNA. Toxicology 221, 179–186.

Audebert, M., Charbonnier, J.B., Boiteux, S., Radicella, J.P., 2002. Mitochondrial targeting of human 8-oxoguanine DNA glycosylase hOGG1 is impaired by a somatic mutation found in kidney cancer. DNA Repair 1, 497–505.

Bakman, A.S., Boichenko, S.S., Kuznetsova, A.A., Ishchenko, A.A., Saparbaev, M., Kuznetsov, N.A., 2023. The Impact of Human DNA Glycosylases on the Activity of DNA Polymerase β toward Various Base Excision Repair Intermediates. Int. J. Mol. Sci. 24.

Banerjee, D., Mandal, S.M., Das, A., Hegde, M.L., Das, S., Bhakat, K.K., Boldogh, I., Sarkar, P.S., Mitra, S., Hazra, T.K., 2011. Preferential repair of oxidized base damage in the transcribed genes of mammalian cells. J. Biol. Chem. 286, 6006–6016.

Baptiste, B.A., Katchur, S.R., Fivenson, E.M., Croteau, D.L., Rumsey, W.L., Bohr, V.A., 2018. Enhanced mitochondrial DNA repair of the common disease-associated variant, Ser326Cys, of hOGG1 through small molecule intervention. Free Radic. Biol. & Med. 124, 149–162.

Boldogh, I., Milligan, D., Lee, M.S., Bassett, H., Lloyd, R.S., McCullough, A.K., 2001. hMYH cell cycle-dependent expression, subcellular localization and association with replication foci: evidence suggesting replication-coupled repair of adenine:8-oxoguanine mispairs. Nucleic Acids Res 29, 2802–2809.

Bordin, D.L., Grooms, K., Montaldo, N.P., Fordyce Martin, S.L., Sætrom, P., Samson, L.D., Bjørås, M., van Loon, B., 2024. Loss of alkyladenine DNA glycosylase alters gene expression in the developing mouse brain and leads to reduced anxiety and improved memory. DNA Repair (Amst.) 135, 103632.

Bradley-Whitman, M.A., Timmons, M.D., Beckett, T.L., Murphy, M.P., Lynn, B.C., Lovell, M.A., 2014. Nucleic acid oxidation: an early feature of Alzheimer's disease. J. Neurochem. 128, 294–304.

Brazel, C.Y., Rao, M.S., 2004. Aging and neuronal replacement. Ageing Res. Rev. 3, 465–483.

Brooks, S.C., Adhikary, S., Rubinson, E.H., Eichman, B.F., 2013. Recent advances in the structural mechanisms of DNA glycosylases. Biochim Biophys. Acta 1834, 247–271.

Caldecott, K.W., 2022. DNA single-strand break repair and human genetic disease. Trends Cell Biol. 32, 733–745.

Canugovi, C., Misiak, M., Ferrarelli, L.K., Croteau, D.L., Bohr, V.A., 2013. The role of DNA repair in brain related disease pathology. DNA Repair 12, 578–587.

Cardozo-Pelaez, F., Sanchez-Contreras, M., Nevin, A.B., 2012. Ogg1 null mice exhibit age-associated loss of the nigrostriatal pathway and increased sensitivity to MPTP. Neurochem. Int 61, 721–730.

Carter, R.J., Parsons, J.L., 2016. Base Excision Repair, a Pathway Regulated by Posttranslational Modifications. Mol. Cell Biol. 36, 1426–1437.

Ceylan, D., Tuna, G., Kirkali, G., Tunca, Z., Can, G., Arat, H.E., Kant, M., Dizdaroglu, M., Özerdem, A., 2018. Oxidatively-induced DNA damage and base excision repair in euthymic patients with bipolar disorder. DNA Repair 65, 64–72.

Chen, L., Huan, X., Gao, X.D., Yu, W.H., Xiao, G.H., Li, T.F., Wang, Z.Y., Zhang, Y.C., 2022. Biological Functions of the DNA Glycosylase NEIL3 and Its Role in Disease Progression Including Cancer. Cancers (Basel) 14.

Chen, Y.H., Kuo, Y.Y., You, Y.Q., Lin, Y.T., Chen, P.C., 2023. Endonuclease VIII-like 1 deficiency potentiates nigrostriatal dopaminergic neuron degeneration in a male mouse model of Parkinson's disease. J. Neurochem. 165, 741–755.

Chiorcea-Paquim, A.M., 2022. 8-oxoguanine and 8-oxodeoxyguanosine Biomarkers of Oxidative DNA Damage: A Review on HPLC-ECD Determination. Mol. (Basel Switz.) 27.

Chow, H.M., Herrup, K., 2015. Genomic integrity and the ageing brain. Nat. Rev. Neurosci. 16, 672–684.

Chu, J.J., Ji, W.B., Zhuang, J.H., Gong, B.F., Chen, X.H., Cheng, W.B., Liang, W.D., Li, G. R., Gao, J., Yin, Y., 2022. Nanoparticles-based anti-aging treatment of Alzheimer's disease. Drug Deliv. 29, 2100–2116.

Conlon, S.G., Khuu, C., Trasviña-Arenas, C.H., Xia, T., Hamm, M.L., Raetz, A.G., David, S. S., 2024. Cellular Repair of Synthetic Analogs of Oxidative DNA Damage Reveals a Key Structure-Activity Relationship of the Cancer-Associated MUTYH DNA Repair Glycosylase. ACS Cent. Sci. 10, 291–301.

Das, S., 2025. Alzheimer's disease basics: we all should know. Neurol. Res. 1–30.

Delint-Ramirez, I., Madabhushi, R., 2025. DNA damage and its links to neuronal aging and degeneration. Neuron 113, 7–28.

Demple, B., Sung, J.-S., 2005. Molecular and biological roles of Ape1 protein in mammalian base excision repair. DNA Repair 4, 1442–1449.

Dizdaroglu, M., 2005. Base-excision repair of oxidative DNA damage by DNA glycosylases. Mutat. Res. /Fundam. Mol. Mech. Mutagen. 591, 45–59.

Donley, N., Jaruga, P., Coskun, E., Dizdaroglu, M., McCullough, A.K., Lloyd, R.S., 2015. Small Molecule Inhibitors of 8-Oxoguanine DNA Glycosylase-1 (OGG1). ACS Chem. Biol. 10, 2334–2343.

Dou, H., Mitra, S., Hazra, T.K., 2003. Repair of oxidized bases in DNA bubble structures by human DNA glycosylases NEIL1 and NEIL2. J. Biol. Chem. 278, 49679–49684.

Ebrahimkhani, M.R., Daneshmand, A., Mazumder, A., Allocca, M., Calvo, J.A., Abolhassani, N., Jhun, I., Muthupalani, S., Ayata, C., Samson, L.D., 2014. Aag-initiated base excision repair promotes ischemia reperfusion injury in liver, brain, and kidney. Proc. Natl. Acad. Sci. USA 111, E4878–4886.

Egiazarian, M.A., Strømstad, S., Sakshaug, T., Nunez-Nescolarde, A.B., Bethge, N., Bjørås, M., Scheffler, K., 2022. Age- and sex-dependent effects of DNA glycosylase Neil3 on amyloid pathology, adult neurogenesis, and memory in a mouse model of Alzheimer's disease. Free Radic. Biol. Med 193, 685–693.

El Gaamouch, F., Chen, F., Ho, L., Lin, H.Y., Yuan, C., Wong, J., Wang, J., 2022. Benefits of dietary polyphenols in Alzheimer's disease. Front. Aging Neurosci. 14, 1019942.

Englander, E.W., Hu, Z., Sharma, A., Lee, H.M., Wu, Z.H., Greeley, G.H., 2002. Rat MYH, a glycosylase for repair of oxidatively damaged DNA, has brain-specific isoforms that localize to neuronal mitochondria. J. Neurochem. 83, 1471–1480.

Fan, J., Wilson, D.M., 2005. Protein–protein interactions and posttranslational modifications in mammalian base excision repair. Free Radic. Biol. Med. 38, 1121–1138.

Frosina, G., Fortini, P., Rossi, O., Carrozzino, F., Raspaglio, G., Cox, L.S., Lane, D.P., Abbondandolo, A., Dogliotti, E., 1996. Two Pathways for Base Excision Repair in Mammalian Cells (*). J. Biol. Chem. 271, 9573–9578.

Fujikawa, D.G., 2023. Programmed mechanisms of status epilepticus-induced neuronal necrosis. Epilepsia Open 8 (1), S25–s34.

Fukae, J., Takanashi, M., Kubo, S., Nishioka, K., Nakabeppu, Y., Mori, H., Mizuno, Y., Hattori, N., 2005. Expression of 8-oxoguanine DNA glycosylase (OGG1) in Parkinson's disease and related neurodegenerative disorders. Acta Neuropathol. 109, 256–262.

Gabbita, S.P., Lovell, M.A., Markesbery, W.R., 1998. Increased nuclear DNA oxidation in the brain in Alzheimer's disease. J. Neurochem. 71, 2034–2040.

Geng, W., Li, P., Zhang, G., Zhong, R., Xu, L., Kang, L., Liu, X., Wu, M., Ji, M., Guan, H., 2025. Targeted Activation of OGG1 Inhibits Paraptosis in Lens Epithelial Cells of Early Age-Related Cortical Cataract. Invest. Ophthalmol. & Vis. Sci. 66, 29.

González-Díaz, C.A., Suárez-Souto, M.A., Pérez-Soto, E., Gómez-López, M., Munguía-Cervantes, J.E., Pérez-Vielma, N.M., Sánchez-Monroy, V., 2024. The Human 8-oxoG DNA Glycosylase 1 (OGG1) Ser326Cys Polymorphism in Infertile Men. Biomedicines 12.

Götz, J., Ittner, A., Ittner, L.M., 2012. Tau-targeted treatment strategies in Alzheimer's disease. Br. J. Pharm. 165, 1246–1259.

Gupta, S., You, P., SenGupta, T., Nilsen, H., Sharma, K., 2021. Crosstalk between Different DNA Repair Pathways Contributes to Neurodegenerative Diseases. Biology.

Hajnády, Z., Nagy-Pénzes, M., Demény, M.A., Kovács, K., El-Hamoly, T., Maléth, J., Hegyi, P., Polgár, Z., Hegedűs, C., Virág, L., 2022. OGG1 Inhibition Reduces Acinar Cell Injury in a Mouse Model of Acute Pancreatitis. Biomedicines 10.

Hang, B., Singer, B., Margison, G.P., Elder, R.H., 1997. Targeted deletion of alkylpurine-DNA-N-glycosylase in mice eliminates repair of 1,N6-ethenoadenine and hypoxanthine but not of 3,N4-ethenocytosine or 8-oxoguanine. Proc. Natl. Acad. Sci. USA 94, 12869–12874.

Hank, E.C., D'Arcy-Evans, N.D., Scaletti, E.R., Benítez-Buelga, C., Wallner, O., Ortis, F., Zhou, K., Meng, L., Del Prado, A., Calvo, P., Almlöf, I., Wiita, E., Nierlin, K., Košenina, S., Krämer, A., Eddershaw, A., Kehler, M., Long, M., Jemth, A.S.,

Dawson, H., Stewart, J., Dickey, A., Astorga, M.E., Varga, M., Homan, E.J., Scobie, M., Knapp, S., Sastre, L., Stenmark, P., de Vega, M., Helleday, T., Michel, M., 2026. Nucleobase catalysts for the enzymatic activation of 8-oxoguanine DNA glycosylase 1. RSC Chem. Biol. 7, 169–181.
Hanna, B.M.F., Helleday, T., Mortusewicz, O., 2020. OGG1 Inhibitor TH5487 Alters OGG1 Chromatin Dynamics and Prevents Incisions. Biomolecules 10.
Hans, F., Senarisoy, M., Bhaskar Naidu, C., Timmins, J., 2020. Focus on DNA Glycosylases-A Set of Tightly Regulated Enzymes with a High Potential as Anticancer Drug Targets. Int J. Mol. Sci. 21.
Hashiguchi, K., Stuart, J.A., de Souza-Pinto, N.C., Bohr, V.A., 2004. The C-terminal alphaO helix of human Ogg1 is essential for 8-oxoguanine DNA glycosylase activity: the mitochondrial beta-Ogg1 lacks this domain and does not have glycosylase activity. Nucleic Acids Res 32, 5596–5608.
Hazra, T.K., Izumi, T., Boldogh, I., Imhoff, B., Kow, Y.W., Jaruga, P., Dizdaroglu, M., Mitra, S., 2002a. Identification and characterization of a human DNA glycosylase for repair of modified bases in oxidatively damaged DNA. Proc. Natl. Acad. Sci. USA 99, 3523–3528.
Hazra, T.K., Kow, Y.W., Hatahet, Z., Imhoff, B., Boldogh, I., Mokkapati, S.K., Mitra, S., Izumi, T., 2002b. Identification and characterization of a novel human DNA glycosylase for repair of cytosine-derived lesions. J. Biol. Chem. 277, 30417–30420.
Hegde, M.L., Bharathi, P., Suram, A., Venugopal, C., Jagannathan, R., Poddar, P., Srinivas, P., Sambamurti, K., Rao, K.J., Scancar, J., Messori, L., Zecca, L., Zatta, P., 2009. Challenges associated with metal chelation therapy in Alzheimer's disease. J. Alzheimers Dis. 17, 457–468.
Hegde, M.L., Hegde, P.M., Bellot, L.J., Mandal, S.M., Hazra, T.K., Li, G.M., Boldogh, I., Tomkinson, A.E., Mitra, S., 2013. Prereplicative repair of oxidized bases in the human genome is mediated by NEIL1 DNA glycosylase together with replication proteins. Proc. Natl. Acad. Sci. USA 110, E3090–3099.
Hegde, M.L., Hegde, P.M., Holthauzen, L.M., Hazra, T.K., Rao, K.S., Mitra, S., 2010. Specific Inhibition of NEIL-initiated repair of oxidized base damage in human genome by copper and iron: potential etiological linkage to neurodegenerative diseases. J. Biol. Chem. 285, 28812–28825.
Hitomi, K., Iwai, S., Tainer, J.A., 2007. The intricate structural chemistry of base excision repair machinery: implications for DNA damage recognition, removal, and repair. DNA Repair (Amst.) 6, 410–428.
Hooper, C., Meimaridou, E., Tavassoli, M., Melino, G., Lovestone, S., Killick, R., 2007. p53 is upregulated in Alzheimer's disease and induces tau phosphorylation in HEK293a cells. Neurosci. Lett. 418, 34–37.
Horton, J.K., Prasad, R., Hou, E., Wilson, S.H., 2000. Protection against Methylation-induced Cytotoxicity by DNA Polymerase;-Dependent Long Patch Base Excision Repair *. J. Biol. Chem. 275, 2211–2218.
Hu, M., Li, X., Fan, D., Yu, L., Ren, F., Wu, J., Mi, J., Zheng, Y., Zhou, X., Qin, D., Wu, A., 2026. NAD(+) supplementation augments the efficacy of the PARP1 inhibitor PJ34 in a 6-OHDA-induced model of Parkinson's disease. Genes & Dis. 13, 101783.
Hu, J., de Souza-Pinto, N.C., Haraguchi, K., Hogue, B.A., Jaruga, P., Greenberg, M.M., Dizdaroglu, M., Bohr, V.A., 2005. Repair of formamidopyrimidines in DNA involves different glycosylases: role of the OGG1, NTH1, and NEIL1 enzymes. J. Biol. Chem. 280, 40544–40551.
Hua, A.B., Sweasy, J.B., 2024. Functional roles and cancer variants of the bifunctional glycosylase NEIL2. Environ. Mol. Mutagen. 65 (1), 40–56.
Huffman, J.L., Sundheim, O., Tainer, J.A., 2005. DNA base damage recognition and removal: New twists and grooves. Mutat. Res. /Fundam. Mol. Mech. Mutagen. 577, 55–76.
Hwang, Y., Kang, S.J., Kang, J., Choi, J., Kim, S.J., Jang, S., 2025b. DNA repair and disease: insights from the human DNA glycosylase NEIL family. Exp. & Mol. Med. 57, 524–532.
Hwang, Y., Kang, S.-J., Kang, J., Choi, J., Kim, S.-J., Jang, S., 2025a. DNA repair and disease: insights from the human DNA glycosylase NEIL family. Exp. & Mol. Med. 57, 524–532.
Iida, T., Furuta, A., Nishioka, K., Nakabeppu, Y., Iwaki, T., 2002. Expression of 8-oxoguanine DNA glycosylase is reduced and associated with neurofibrillary tangles in Alzheimer's disease brain. Acta Neuropathol. 103, 20–25.
Izumi, T., Tatsuka, M., Tano, K., Asano, M., Mitra, S., 1997. Molecular cloning and characterization of the promoter of the human N-methylpurine-DNA glycosylase (MPG) gene. Carcinogenesis 18, 1837–1839.
Jacobs, A.C., Calkins, M.J., Jadhav, A., Dorjsuren, D., Maloney, D., Simeonov, A., Jaruga, P., Dizdaroglu, M., McCullough, A.K., Lloyd, R.S., 2013. Inhibition of DNA glycosylases via small molecule purine analogs. PloS One 8, e81667.
Jacobs, A.L., Schär, P., 2012. DNA glycosylases: in DNA repair and beyond. Chromosoma 121, 1–20.
Jagannatha, R., Rao, R.V., Shanmugavelu, P., Menon, R., 1999. Trace elements in Alzheimer's disease brain: A new hypothesis. Alzheimer's. Rep. 2, 241–246.
Jaruga, P., Kant, M., Luzadder, M.M., Lloyd, R.S., Boldogh, I., Dizdaroglu, M., 2025. Inhibition by 4-(4-Bromo-2-oxo-3H-benzimidazol-1-yl)-N-(4-iodophenyl)piperidine-1-carboxamide (TH5487) of the Activity of Human 8-Oxoguanine DNA Glycosylase-1 (OGG1) for the Excision of 2,6-Diamino-4-hydroxy-5-formamidopyrimidine, 4,6-Diamino-5-formamidopyrimidine, and 8-Oxoguanine from Oxidatively Damaged DNA. Biochemistry 64, 1788–1796.
Johnson, M.D., Kinoshita, Y., Xiang, H., Ghatan, S., Morrison, R.S., 1999. Contribution of p53-dependent caspase activation to neuronal cell death declines with neuronal maturation. J. Neurosci. 19, 2996–3006.
Kant, M., Tahara, Y.K., Jaruga, P., Coskun, E., Lloyd, R.S., Kool, E.T., Dizdaroglu, M., 2021. Inhibition by Tetrahydroquinoline Sulfonamide Derivatives of the Activity of Human 8-Oxoguanine DNA Glycosylase (OGG1) for Several Products of Oxidatively induced DNA Base Lesions. ACS Chem. Biol. 16, 45–51.
Kirova, A.M., Bays, R.B., Lagalwar, S., 2015. Working memory and executive function decline across normal aging, mild cognitive impairment, and Alzheimer's disease. Biomed. Res Int 2015, 748212.
Krokan, H.E., Drabløs, F., Slupphaug, G., 2002. Uracil in DNA–occurrence, consequences and repair. Oncogene 21, 8935–8948.
Lagunas-Rangel, F.A., 2022. SIRT7 in the aging process. Cell. Mol. life Sci. CMLS 79, 297.
Lantyer, R., Baracho, N., Camins, A., Ettcheto Arriola, M., 2021. Pharmacological drug strategies in Alzheimer's Disease. Rev. Neurociências 29.
Lau, A.Y., Schärer, O.D., Samson, L., Verdine, G.L., Ellenberger, T., 1998. Crystal structure of a human alkylbase-DNA repair enzyme complexed to DNA: mechanisms for nucleotide flipping and base excision. Cell 95, 249–258.
Lee, C.Y., Delaney, J.C., Kartalou, M., Lingaraju, G.M., Maor-Shoshani, A., Essigmann, J. M., Samson, L.D., 2009. Recognition and processing of a new repertoire of DNA substrates by human 3-methyladenine DNA glycosylase (AAG). Biochemistry 48, 1850–1861.
Lee, T.H., Kang, T.H., 2019. DNA Oxidation and Excision Repair Pathways. Int J. Mol. Sci. 20.
Levin, D.S., Vijayakumar, S., Liu, X., Bermudez, V.P., Hurwitz, J., Tomkinson, A.E., 2004. A Conserved Interaction between the Replicative Clamp Loader and DNA Ligase in Eukaryotes: IMPLICATIONS FOR OKAZAKI FRAGMENT JOINING *. J. Biol. Chem. 279, 55196–55201.
Li, N., Wang, J., Wallace, S.S., Chen, J., Zhou, J., D'Andrea, A.D., 2020. Cooperation of the NEIL3 and Fanconi anemia/BRCA pathways in interstrand crosslink repair. Nucleic Acids Res. 48, 3014–3028.
Li, N., Xu, Y., Chen, H., Chen, L., Zhang, Y., Yu, T., Yao, R., Chen, J., Fu, Q., Zhou, J., Wang, J., 2022. NEIL3 contributes to the Fanconi anemia/BRCA pathway by promoting the downstream double-strand break repair step. Cell Rep. 41, 111600.
Liu, M., Bandaru, V., Bond, J.P., Jaruga, P., Zhao, X., Christov, P.P., Burrows, C.J., Rizzo, C.J., Dizdaroglu, M., Wallace, S.S., 2010. The mouse ortholog of NEIL3 is a functional DNA glycosylase in vitro and in vivo. Proc. Natl. Acad. Sci. USA 107, 4925–4930.
Liu, M., Bandaru, V., Holmes, A., Averill, A.M., Cannan, W., Wallace, S.S., 2012. Expression and purification of active mouse and human NEIL3 proteins. Protein Expr. Purif. 84, 130–139.
López-Gil, L., Pascual-Ahuir, A., Proft, M., 2023. Genomic Instability and Epigenetic Changes during Aging. Int. J. Mol. Sci. 24.
Lovell, M.A., Gabbita, S.P., Markesbery, W.R., 1999. Increased DNA oxidation and decreased levels of repair products in Alzheimer's disease ventricular CSF. J. Neurochem. 72, 771–776.
Lovell, M.A., Markesbery, W.R., 2007. Oxidative DNA damage in mild cognitive impairment and late-stage Alzheimer's disease. Nucleic Acids Res 35, 7497–7504.
Lovell, M.A., Soman, S., Bradley, M.A., 2011. Oxidatively modified nucleic acids in preclinical Alzheimer's disease (PCAD) brain. Mech. Ageing Dev. 132, 443–448.
Lovell, M.A., Xie, C., Markesbery, W.R., 2000. Decreased base excision repair and increased helicase activity in Alzheimer's disease brain. Brain Res. 855, 116–123.
Madabhushi, R., Pan, L., Tsai, L.H., 2014. DNA damage and its links to neurodegeneration. Neuron 83, 266–282.
Maher, R.L., Vallur, A.C., Feller, J.A., Bloom, L.B., 2007. Slow base excision by human alkyladenine DNA glycosylase limits the rate of formation of AP sites and AP endonuclease 1 does not stimulate base excision. DNA Repair (Amst.) 6, 71–81.
Mangerich, A., Bürkle, A., 2012. Pleiotropic cellular functions of PARP1 in longevity and aging: genome maintenance meets inflammation. Oxid. Med Cell Longev. 2012, 321653.
Maynard, S., Fang, E.F., Scheibye-Knudsen, M., Croteau, D.L., Bohr, V.A., 2015. DNA Damage, DNA Repair, Aging, and Neurodegeneration. Cold Spring Harb. Perspect. Med 5.
McCullough, A.K., Minko, I.G., Luzadder, M.M., Zuckerman, J.T., Vartanian, V.L., Jaruga, P., Dizdaroglu, M., Lloyd, R.S., 2025. Role of NEIL1 in genome maintenance. DNA Repair 148, 103820.
McKinnon, P.J., 2013. Maintaining genome stability in the nervous system. Nat. Neurosci. 16, 1523–1529.
Menoni, H., Hoeijmakers, J.H., Vermeulen, W., 2012. Nucleotide excision repair-initiating proteins bind to oxidative DNA lesions in vivo. J. Cell Biol. 199, 1037–1046.
Menoni, H., Wienholz, F., Theil, A.F., Janssens, R.C., Lans, H., Campalans, A., Radicella, J.P., Marteijn, J.A., Vermeulen, W., 2018. The transcription-coupled DNA repair-initiating protein CSB promotes XRCC1 recruitment to oxidative DNA damage. Nucleic Acids Res. 46, 7747–7756.
Michel, M., Benítez-Buelga, C., Calvo, P.A., Hanna, B.M.F., Mortusewicz, O., Masuyer, G., Davies, J., Wallner, O., Sanjiv, K., Albers, J.J., Castañeda-Zegarra, S., Jemth, A.S., Visnes, T., Sastre-Perona, A., Danda, A.N., Homan, E.J., Marimuthu, K., Zhenjun, Z., Chi, C.N., Sarno, A., Wiita, E., von Nicolai, C., Komor, A.J., Rajagopal, V., Müller, S., Hank, E.C., Varga, M., Scaletti, E.R., Pandey, M., Karsten, S., Haslene-Hox, H., Loevenich, S., Marttila, P., Rasti, A., Mamonov, K., Ortis, F., Schömberg, F., Loseva, O., Stewart, J., D'Arcy-Evans, N., Koolmeister, T., Henriksson, M., Michel, D., de Ory, A., Acero, L., Calvete, O., Scobie, M., Hertweck, C., Vilotijevic, I., Kalderén, C., Osorio, A., Perona, R., Stolz, A., Stenmark, P., Berglund, U.W., de Vega, M., Helleday, T., 2022. Small-molecule activation of OGG1 increases oxidative DNA damage repair by gaining a new function. Science (New York N. Y.) 376, 1471–1476.
Mizuno, Y., Abolhassani, N., Mazzei, G., Sakumi, K., Saito, T., Saido, T.C., Ninomiya, T., Iwaki, T., Yamasaki, R., Kira, J.I., Nakabeppu, Y., 2021. MUTYH Actively Contributes to Microglial Activation and Impaired Neurogenesis in the Pathogenesis of Alzheimer's Disease. Oxid. Med. Cell. Longev. 2021, 8635088.
Mizuno, Y., Abolhassani, N., Mazzei, G., Saito, T., Saido, T.C., Yamasaki, R., Kira, J.I., Nakabeppu, Y., 2022. Deficiency of MTH1 and/or OGG1 increases the accumulation

of 8-oxoguanine in the brain of the App(NL-G-F/NL-G-F) knock-in mouse model of Alzheimer's disease, accompanied by accelerated microgliosis and reduced anxiety-like behavior. Neurosci. Res. 177, 118–134.
Moneim, A.E., 2015. Oxidant/Antioxidant imbalance and the risk of Alzheimer's disease. Curr. Alzheimer Res 12, 335–349.
Montaldo, N.P., Bordin, D.L., Brambilla, A., Rösinger, M., Fordyce Martin, S.L., Bjørås, K., Bradamante, S., Aas, P.A., Furrer, A., Olsen, L.C., Kunath, N., Otterlei, M., Sætrom, P., Bjørås, M., Samson, L.D., van Loon, B., 2019. Alkyladenine DNA glycosylase associates with transcription elongation to coordinate DNA repair with gene expression. Nat. Commun. 10, 5460.
Mullins, E.A., Rodriguez, A.A., Bradley, N.P., Eichman, B.F., 2019. Emerging Roles of DNA Glycosylases and the Base Excision Repair Pathway. Trends Biochem Sci. 44, 765–781.
Murakami, T., Nagai, M., Miyazaki, K., Morimoto, N., Ohta, Y., Kurata, T., Takehisa, Y., Kamiya, T., Abe, K., 2007. Early decrease of mitochondrial DNA repair enzymes in spinal motor neurons of presymptomatic transgenic mice carrying a mutant SOD1 gene. Brain Res 1150, 182–189.
Nakabeppu, Y., 2017. Neurodegeneration Caused by Accumulation of an Oxidized Base Lesion, 8-oxoguanine, in Nuclear and Mitochondrial DNA: From Animal Models to Human Diseases. Mol. Mech. Role Dis. Dev. Ther. Des. 523–556.
Nishimura, S., 2001. Mammalian Ogg1/Mmh gene plays a major role in repair of the 8-hydroxyguanine lesion in DNA. Prog. Nucleic Acid. Res Mol. Biol. 68, 107–123.
Nishioka, K., Ohtsubo, T., Oda, H., Fujiwara, T., Kang, D., Sugimachi, K., Nakabeppu, Y., 1999. Expression and differential intracellular localization of two major forms of human 8-oxoguanine DNA glycosylase encoded by alternatively spliced OGG1 mRNAs. Mol. Biol. Cell 10, 1637–1652.
Oka, S., Leon, J., Sakumi, K., Abolhassani, N., Sheng, Z., Tsuchimoto, D., LaFerla, F.M., Nakabeppu, Y., 2021. MTH1 and OGG1 maintain a low level of 8-oxoguanine in Alzheimer's brain, and prevent the progression of Alzheimer's pathogenesis. Sci. Rep. 11, 5819.
Oka, S., Nakabeppu, Y., 2011. DNA glycosylase encoded by MUTYH functions as a molecular switch for programmed cell death under oxidative stress to suppress tumorigenesis. Cancer Sci. 102, 677–682.
Pao, P.C., Patnaik, D., Watson, L.A., Gao, F., Pan, L., Wang, J., Adaikkan, C., Penney, J., Cam, H.P., Huang, W.C., Pantano, L., Lee, A., Nott, A., Phan, T.X., Gjoneska, E., Elmsaouri, S., Haggarty, S.J., Tsai, L.H., 2020. HDAC1 modulates OGG1-initiated oxidative DNA damage repair in the aging brain and Alzheimer's disease. Nat. Commun. 11, 2484.
Parker, A.R., Eshleman, J.R., 2003. Human MutY: gene structure, protein functions and interactions, and role in carcinogenesis. Cell Mol. Life Sci. 60, 2064–2083.
Parlanti, E., D'Errico, M., Degan, P., Calcagnile, A., Zijno, A., van der Pluijm, I., van der Horst, G.T., Biard, D.S., Dogliotti, E., 2012. The cross talk between pathways in the repair of 8-oxo-7,8-dihydroguanine in mouse and human cells. Free Radic. Biol. Med. 53, 2171–2177.
Poot, M., 2025. Molecular mechanisms of proliferative senescence and genomic instability in werner syndrome and the WRN gene network. Cytogenet. Genome Res. 1–20.
Prakash, A., Doublié, S., Wallace, S.S., 2012. The Fpg/Nei family of DNA glycosylases: substrates, structures, and search for damage. Prog. Mol. Biol. Transl. Sci. 110, 71–91.
Rangaswamy, S., Pandey, A., Mitra, S., Hegde, M.L., 2017. Pre-replicative repair of oxidized bases maintains fidelity in mammalian genomes: the cowcatcher role of NEIL1 DNA glycosylase. Genes 8.
Raper, A.T., Maxwell, B.A., Suo, Z., 2021. Dynamic processing of a common oxidative DNA lesion by the first two enzymes of the base excision repair pathway. J. Mol. Biol. 433, 166811.
Regnell, C.E., Hildrestrand, G.A., Sejersted, Y., Medin, T., Moldestad, O., Rolseth, V., Krokeide, S.Z., Suganthan, R., Luna, L., Bjørås, M., Bergersen, L.H., 2012. Hippocampal adult neurogenesis is maintained by Neil3-dependent repair of oxidative DNA lesions in neural progenitor cells. Cell Rep. 2, 503–510.
Robson, C.N., Hickson, I.D., 1991. Isolation of cDNA clones encoding a human apurinic/apyrimidinic endonuclease that corrects DNA repair and mutagenesis defects in E. coli xth (exonuclease III) mutants. Nucleic Acids Res 19, 5519–5523.
Sassa, A., Odagiri, M., 2020. Understanding the sequence and structural context effects in oxidative DNA damage repair. DNA Repair 93, 102906.
Schärer, O., 2001. Chemical biology of mammalian DNA repair. CHIMIA Int. J. Chem. 55, 340–344.
Sedelnikova, O.A., Horikawa, I., Zimonjic, D.B., Popescu, N.C., Bonner, W.M., Barrett, J. C., 2004. Senescing human cells and ageing mice accumulate DNA lesions with unrepairable double-strand breaks. Nat. Cell Biol. 6, 168–170.
Shanbhag, N.M., Evans, M.D., Mao, W., Nana, A.L., Seeley, W.W., Adame, A., Rissman, R. A., Masliah, E., Mucke, L., 2019. Early neuronal accumulation of DNA double strand breaks in Alzheimer's disease. Acta Neuropathol. Commun. 7, 77.
Shao, C., Xiong, S., Li, G.M., Gu, L., Mao, G., Markesbery, W.R., Lovell, M.A., 2008. Altered 8-oxoguanine glycosylase in mild cognitive impairment and late-stage Alzheimer's disease brain. Free Radic. Biol. Med 45, 813–819.
Sheng, Z., Oka, S., Tsuchimoto, D., Abolhassani, N., Nomaru, H., Sakumi, K., Yamada, H., Nakabeppu, Y., 2012. 8-Oxoguanine causes neurodegeneration during MUTYH-mediated DNA base excision repair. J. Clin. Invest 122, 4344–4361.
Shinmura, K., Kasai, H., Sasaki, A., Sugimura, H., Yokota, J., 1997. 8-hydroxyguanine (7,8-dihydro-8-oxoguanine) DNA glycosylase and AP lyase activities of hOGG1 protein and their substrate specificity. Mutat. Res. /DNA Repair 385, 75–82.
Sliwinska, A., Kwiatkowski, D., Czarny, P., Toma, M., Wigner, P., Drzewoski, J., Fabianowska-Majewska, K., Szemraj, J., Maes, M., Galecki, P., Sliwinski, T., 2016. The levels of 7,8-dihydrodeoxyguanosine (8-oxoG) and 8-oxoguanine DNA glycosylase 1 (OGG1) - A potential diagnostic biomarkers of Alzheimer's disease. J. Neurol. Sci. 368, 155–159.
de Sousa, M.M.L., Ye, J., Luna, L., Hildrestrand, G., Bjørås, K., Scheffler, K., Bjørås, M., 2021. Impact of oxidative DNA damage and the role of DNA glycosylases in neurological dysfunction. Int J. Mol. Sci. 22.
Stivers, J.T., 2004. Site-specific DNA damage recognition by enzyme-induced base flipping. Prog. Nucleic Acid. Res Mol. Biol. 77, 37–65.
Stivers, J.T., Jiang, Y.L., 2003. A mechanistic perspective on the chemistry of DNA repair glycosylases. Chem. Rev. 103, 2729–2760.
Su, C., Chen, Y., Chen, K., Li, W., Tang, H., 2020. Inhibitory potency of 4- substituted sampangine derivatives toward Cu(2+) mediated aggregation of amyloid β-peptide, oxidative stress, and inflammation in Alzheimer's disease. Neurochem. Int. 139, 104794.
Tahara, Y.K., Auld, D., Ji, D., Beharry, A.A., Kietrys, A.M., Wilson, D.L., Jimenez, M., King, D., Nguyen, Z., Kool, E.T., 2018. Potent and selective inhibitors of 8-oxoguanine DNA glycosylase. J. Am. Chem. Soc. 140, 2105–2114.
Tahara, Y.K., Kietrys, A.M., Hebenbrock, M., Lee, Y., Wilson, D.L., Kool, E.T., 2019. Dual Inhibitors of 8-Oxoguanine Surveillance by OGG1 and NUDT1. ACS Chem. Biol. 14, 2606–2615.
Taherzadeh-Fard, E., Saft, C., Wieczorek, S., Epplen, J.T., Arning, L., 2010. Age at onset in Huntington's disease: replication study on the associations of ADORA2A, HAP1 and OGG1. Neurogenetics 11, 435–439.
Takao, M., Aburatani, H., Kobayashi, K., Yasui, A., 1998. Mitochondrial targeting of human DNA glycosylases for repair of oxidative DNA damage. Nucleic Acids Res 26, 2917–2922.
Tao, H., Shinmura, K., Hanaoka, T., Natsukawa, S., Shaura, K., Koizumi, Y., Kasuga, Y., Ozawa, T., Tsujinaka, T., Li, Z., Yamaguchi, S., Yokota, J., Sugimura, H., Tsugane, S., 2004. A novel splice-site variant of the base excision repair gene MYH is associated with production of an aberrant mRNA transcript encoding a truncated MYH protein not localized in the nucleus. Carcinogenesis 25, 1859–1866.
Thayer, M.M., Ahern, H., Xing, D., Cunningham, R.P., Tainer, J.A., 1995. Novel DNA binding motifs in the DNA repair enzyme endonuclease III crystal structure. EMBO J. 14, 4108–4120.
Torgasheva, N.A., Diatlova, E.A., Grin, I.R., Endutkin, A.V., Mechetin, G.V., Vokhtantsev, I.P., Yudkina, A.V., Zharkov, D.O., 2022. Noncatalytic Domains in DNA Glycosylases. Int. J. Mol. Sci. 23.
Trasviña-Arenas, C.H., Dissanayake, U.C., Tamayo, N., Hashemian, M., Lin, W.-J., Demir, M., Hoyos-Gonzalez, N., Fisher, A.J., Cisneros, G.A., Horvath, M.P., David, S. S., 2025. Structure of human MUTYH and functional profiling of cancer-associated variants reveal an allosteric network between its [4Fe-4S] cluster cofactor and active site required for DNA repair. Nat. Commun. 16, 3596.
Valavanidis, A., Vlachogianni, T., Fiotakis, C., 2009. 8-hydroxy-2′ -deoxyguanosine (8-OHdG): a critical biomarker of oxidative stress and carcinogenesis. J. Environ. Sci. Health C. Environ. Carcinog. Ecotoxicol. Rev. 27, 120–139.
Vickers, M.A., Vyas, P., Harris, P.C., Simmons, D.L., Higgs, D.R., 1993. Structure of the human 3-methyladenine DNA glycosylase gene and localization close to the 16p telomere. Proc. Natl. Acad. Sci. USA 90, 3437–3441.
Wang, Z.X., Chen, F., He, B.D., Wang, F.C., Cha, J., Song, Y., Meng, W.Y., Zou, W.Y., Fu, Y.T., Sun, S.X., Sun, Z.Y., Jiang, H.M., Zhao, K.Y., Hou, Y., Shi, J., Xue, J.H., 2025. Direct Sequencing of 5-Methylcytosine and 5-hydroxymethylcytosine at single-base resolution unravels their distinct roles in Alzheimer's disease. Adv. Sci. 12, e07843.
Wang, P., Guliaev, A.B., Elder, R.H., Hang, B., 2006. Alkylpurine-DNA-N-glycosylase excision of 7-(hydroxymethyl)-1,N6-ethenoadenine, a glycidaldehyde-derived DNA adduct. DNA Repair (Amst.) 5, 23–31.
Wang, D., Liu, J., Zhu, Q., Wei, X., Zhang, X., Chen, Q., Zhao, Y., Tang, H., Xu, W., 2024. Ouabain ameliorates Alzheimer's disease-associated neuropathology and cognitive impairment in FAD(4T) mice. Nutrients 16.
Weissman, L., Jo, D.G., Sørensen, M.M., de Souza-Pinto, N.C., Markesbery, W.R., Mattson, M.P., Bohr, V.A., 2007. Defective DNA base excision repair in brain from individuals with Alzheimer's disease and amnestic mild cognitive impairment. Nucleic Acids Res. 35, 5545–5555.
Weissman, L., de Souza-Pinto, N.C., Mattson, M.P., Bohr, V.A., 2009. DNA base excision repair activities in mouse models of Alzheimer's disease. Neurobiol. Aging 30, 2080–2081.
Wilson, D.M., 3rd, Bohr, V.A., 2007. The mechanics of base excision repair, and its relationship to aging and disease. DNA Repair (Amst.) 6, 544–559.
Wu, X., Li, J., Li, X., Hsieh, C.-L., Burgers, P.M.J., Lieber, M.R., 1996. Processing of branched DNA intermediates by a complex of human FEN-1 and PCNA. Nucleic Acids Res. 24, 2036–2043.
Xue, B., Xiao, W., Tian, H., 2020. Nei-like 1 inhibition results in motor dysfunction and promotes inflammation in Parkinson's disease mice model. Biochem Biophys. Res Commun. 521, 245–251.
Yin, Q., Yang, L., 2024. Mechanisms of cognitive impairment associated with cerebral infarction. Zhong nan da xue xue bao. Yi xue Ban. = J. Cent. South Univ. Med. Sci. 49, 1692–1699.
Zhang, Q., Yan, Y., 2023. The role of natural flavonoids on neuroinflammation as a therapeutic target for Alzheimer's disease: a narrative review. Neural Regen. Res. 18, 2582–2591.
Zhao, X., Krishnamurthy, N., Burrows, C.J., David, S.S., 2010. Mutation versus repair: NEIL1 removal of hydantoin lesions in single-stranded, bulge, bubble, and duplex DNA contexts. Biochemistry 49, 1658–1666.
Zhao, B., Yang, Y., Wang, X., Chong, Z., Yin, R., Song, S.H., Zhao, C., Li, C., Huang, H., Sun, B.F., Wu, D., Jin, K.X., Song, M., Zhu, B.Z., Jiang, G., Rendtlew Danielsen, J.M., Xu, G.L., Yang, Y.G., Wang, H., 2014. Redox-active quinones induces genome-wide

DNA methylation changes by an iron-mediated and Tet-dependent mechanism. Nucleic Acids Res. 42, 1593–1605.

Zhou, C., Parsons, J.L., 2020. The radiobiology of HPV-positive and HPV-negative head and neck squamous cell carcinoma. Expert Rev. Mol. Med 22, e3.

Zuo, X., 2025. Mitochondrial imbalance in down syndrome: a driver of accelerated brain aging? Aging Dis. 16, 2674–2694.