Genome Instability & Disease (2022) 3:172–178
https://doi.org/10.1007/s42764-022-00069-y

REVIEW ARTICLE

DNA damage accumulation in aging brain and its links to Alzheimer's disease progression

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Received: 23 January 2022 / Revised: 26 February 2022 / Accepted: 27 February 2022 / Published online: 23 March 2022

Abstract

DNA, which carries information to build the entire human body, is constantly challenged by a variety of endogenous and environmental agents, ultimately leading to mutations and genomic instability, triggering a wide range of cellular responses and causing diverse human diseases. Cells have evolved a variety of DNA repair mechanisms to respond to DNA damage. Recent findings have linked DNA damage in the brain with many neurological diseases. In this review, we discuss how DNA damage in the brain correlates with Alzheimer's disease and how the absence of repair mechanisms accelerates age-related Alzheimer's disease progression. We also review the potential sources of DNA damage, which may be closely associated with cognitive decline in Alzheimer's disease.

Keywords DNA damage repair · Alzheimer's disease · Tau

Introduction

The global population aging trend is increasingly obvious. Aging has caused many health and societal problems, which have in turn caused wide concern among all of society. Alzheimer's disease (AD) is an aging-related neurodegenerative disease with insidious onset and progressive development. Clinically, AD is characterized by memory impairment, aphasia, apraxia, agnosia, visuospatial skill impairment, executive dysfunction, and personality and behavior changes (Masters et al., 2015). Approximately, 50 million people worldwide suffer from AD (Gauthier et al., 2021). As society advances and life expectancy increases, the prevalence of AD will continue to rise, and the number of people with AD is expected to reach 150 million by 2050, which will bring heavy financial and care burdens to families and society (Ren Rujing & Zhihui, 2021).

Aging is well known to be closely related to DNA damage. When DNA is replicated, fragment loss, fractures and other errors inevitably occur that lead to DNA sequence changes. Endogenous chemicals and exogenous environmental factors continue to threaten the stability of cellular genetic material, resulting in a variety of DNA damage events. These DNA damage events may be caused by the effects of ultraviolet radiation, ionizing radiation, plant toxins, toxic agents and reactive oxygen species (ROS) (Finkel & Holbrook, 2000). Up to 10^5 DNA lesions occur daily in active mammalian cells, and it is estimated that spontaneous hydrolysis alone produces approximately 10^4 abasic (mostly apurinic) sites (Lindahl, 1993). Researchers found that DNA damage caused by ionizing radiation can induce senescence in human fibroblasts in cell culture (Wahl & Carr, 2001), suggesting that DNA damage may be directly related with senescence and aging processes.

With increasing age, the DNA scaffolding proteins that help stabilize the genome become less effective, which leads to increased DNA damage (Chen et al., 2007). To combat DNA damage, cells have evolved complex and finely regulated DNA damage repair (DDR) mechanisms to repair the different types of DNA damage, such as base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), non-homologous end joining (NHEJ) and homologous recombination (HR). However, DDR also declines with aging. Impaired DDR makes small mistakes into a large mistake, and the temporary errors become permanent. These errors accumulate to a certain degree and can cause

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substantial damage, eventually leading to a decline in human body function and further inhibiting DNA repair ability, thus leading to a vicious cycle. This vicious cycle happens in many human systems. In this review, we discuss DNA damage in the aging brain and its relationship to AD as well as the intrinsic interaction between DDR malfunctions and AD.

DNA damage in the aging brain and its correlation with age-related neurodegenerative diseases

Aging affects all organs of the body as the basis for neurodegeneration and dementia (Wyss-Coray, 2016). AD and Parkinson's disease (PD) are the most common neurodegenerative diseases among elderly individuals. At the same time, with increasing age, the risk of these diseases is greatly increased (Wyss-Coray, 2016). With the aging of the human body and the declines in DDR, DNA damage gradually accumulates in human cells. Recent findings have suggested that a significant portion of aging phenotypes are associated with DNA damage and are potentially the ultimate cause of aging (Schumacher et al., 2021). DNA damage and genomic instability activate DDR response pathways, triggering cell cycle arrest, apoptosis, and cell senescence, thus accelerating the aging process of individual organisms. In all types of mouse tissue, a marker for DNA double-strand breaks (DSBs), phosphorylation of the Ser-139 residue of the histone variant H2AX (γH2AX), has been observed to accumulate in tissue with age (Sedelnikova et al., 2004b).

For over 20 years, 8-hydroxyguanine (8-OHG), a marker of DNA oxidation levels, has been observed to be elevated, while DNA repair levels are decreased, in the brain and cerebrospinal fluid of older adults and AD patients (Lovell et al., 1999; Mecocci et al., 1994). The oxidative DNA damage level was increased in patients with mild cognitive impairment (MCI) as well as in patients with severe dementia. In these patients, oxidative DNA damage to mitochondrial DNA (mtDNA) and nuclear DNA (nDNA) was observed in various brain regions of the patients (Wang, 2006). Meanwhile, as AD progresses, the level of proteins involved in DNA repair decreases. For instance, BER is one of the major DNA repair pathways and plays an important role in the development and maintenance of the nervous system. Significant BER defects were observed in the brains of AD patients compared with the brains of healthy controls, and the activity of BER-related proteins such as uracil DNA glycosylase, β-ogG1 glycosylase and DNA polymerase β (Polβ) was significantly reduced and inversely proportional to disease severity (Weissman et al., 2007a, 2007b). The levels of γH2AX in astrocytes and neurons in the hippocampus and frontal cortex of AD brains were significantly increased compared to those in normal brains, suggesting that more DSBs had accumulated in AD brains (Shanbhag et al., 2019).

Telomeres are the protective ends of DNA that are crucial to the integrity and stability of the genome. Cells with incomplete chromosomes tend to activate bypasses, leading to cell cycle arrest or death. Shortened telomere length is an indicator of aging cells and predicts an increased risk of age-related diseases. Reductions in telomere length have also been observed in patients with AD. Patients with slow-progressing late-onset AD had shorter telomeres than patients with fast-progressing disease or healthy elderly controls (Gauthier et al., 2021). These results suggest that DNA damage plays an important role in the progression of AD.

The accumulation of H3K4me2 can reportedly restore the balance of gene transcription and prolong the life span of *C. elegans* after restoring the blocked transcription of *C. elegans* (Wang et al., 2020). The poly-ADP ribosylation of histones plays a key role in DNA repair. Poly-ADP ribosylation can reduce the concentration of NAD+, induce apoptosis or indirectly inhibit sirtuin protein, which can affect genome-wide chromatin acetylation, senescence and DNA repair (Fang et al., 2014) and cause changes in gene expression in the brains of elderly mice (Oberdoerffer et al., 2008).

DNA DSB repair in AD

The accumulation of DNA double-strand damage has been observed in aging mice and human cells (Sedelnikova et al., 2004a). In AD model mice, it has been observed that exploring new environments leads to increased DNA double-strand damage in several brain regions, especially those involved in spatial learning and memory pairs (Suberbielle et al., 2013), and elevated levels of γ-H2AX in hippocampal and cortical regions in the brains of AD patients (Myung et al., 2008; Shanbhag et al., 2019), while a trend toward elevation has been found in the brains of patients with MCI in AD (Kirova et al., 2015; Korolev et al., 2016), which suggests that DNA double-strand damage may play an important role in the AD disease process, be an early event and lead to the development of neuronal tangles later in life (Su et al., 1997). In addition to the damage caused by ROS, it has been reported in recent years that DNA double-strand damage may also be associated with neuronal transcriptional activity (Marnef et al., 2017) and that these transcriptional activities occur during learning and memory (Cholewa-Waclaw et al., 2016; West & Greenberg, 2011), suggesting that DNA DSB may be associated with the loss of learning and memory capacity that occurs during AD.

Two major mechanistically distinct pathways exist for DSB repair in mammalian cells: HR and NHEJ. After DNA double-strand damage occurs, the MRN complex (MER11A-NBS1-RAD50) recognizes and binds to the damaged site

and recruits ATM to activate DNA double-strand damage repair. BRCA1-dependent excision of 5′ DNA flanking DNA double-stranded damage sites exposes two single-stranded DNA regions where BRCA2 recruits the DNA recombinase RAD51, which binds to DNA to form nucleoprotein filaments and uses homologous DNA as a template, synthesize new DNA with the help of DNA ligase and endonuclease. Eventually, DNA double-strand damage is repaired (Lord & Ashworth, 2016). The protein expression levels and mRNA levels of key HR factors were observed to decrease in the brains of AD patients and AD mouse models (Shen et al., 2016), indicating HR deficiency may play a role in AD initiation and/or progression. In hAPP-J20 mice, the level of BRCA1 was significantly decreased in the DG region of the hippocampus and Aβ oligomers also could reduce the level of BRCA1 in mouse primary neurons (Suberbielle et al., 2013). DNA double-strand damage also recruits Ku70/Ku80 complexes, which in turn activate and recruit DNA-PKcs to the damage sites, initiating DSB repair via the 53BP1-mediated NHEJ repair pathway. The NHEJ key factor Ku subunit and DNA-PKcs and poly(ADP-ribose) polymerase-1 (PARP1) were found to be absent in cortical regions in the brains of AD (postmortem) patients and may be associated with synaptic loss and memory impairment in AD (Davydov et al., 2003). In PC12 cells, the aggregated Aβ short peptide inhibits DNA-PKcs enzymatic activity while disrupting DSB repair (Culmsee et al., 2001). In addition, the reduction in RAD51 in the hippocampal region of APP/PSEN1 mice was more significant than that in 53BP1 in the AD transgenic mouse model (Yu et al., 2018), suggesting that the HR pathway may play a more important role than other double-strand damage repair pathways in AD.

Defects in BER in AD

The daily production of single-strand breaks (SSBs) is much higher in mammalian cells than that of DSBs (Lindahl, 1993; Vilenchik & Knudson, 2003). The brain is protected from external or environmental genotoxins by the blood–brain barrier, while neurons in the central nervous system have a high metabolic rate (Hegde et al., 2012), and the brain accounts for up to 50% of systemic oxygen consumption as well as 10% of glucose consumption (Magistretti & Pellerin, 1999; Shulman et al., 2004); therefore, endogenous ROS may be a major source of DNA damage in the brains of AD patients (Barja, 2004; Chandrika Canugovi et al., 2014). Oxidative DNA damage has also been observed in the brains of MCI (Bradley-Whitman et al., 2014; Lyras et al., 1997; Wang et al., 2006), preclinical AD (PCAD) (Bradley-Whitman et al., 2014; Lovell et al., 2011) and AD (Gabbita et al., 1998; Lyras et al., 1997) patients.

The repair of oxidative damage to base pairs occurs mainly through the BER pathway. One of the pathways is short-patch BER, where DNA glycosylases recognize and excise bases at the damage site to obtain an abasic site, which is then excised by apurinic/apyrimidinic endonuclease (APE), causing an SSB. This site is excised by Polβ, which then introduces a normal nucleotide, and finally, the normal duplex is obtained by ligating it through the Lig III-XRCC1 complex. Another BER pathway is the NEIL1-3 DNA glycosylase long-patch BER repair pathway. ROS can produce SSBs, which are recognized by poly(ADP) ribose polymerase 1 (PARP1); the ends are then treated with PNKP, actinic dysfunctional ataxia (APTX) or tyrosyl DNA phosphodiesterase 1 (TDP1). Repair is then performed with short-patch BER or long-patch BER (Coppedè et al., 2007; Hart et al., 2001; Weissman, et al., 2007a, 2007b).

Impaired BER pathway function in MCI brains suggests that BER may have an impact on the AD disease process, and reduced 8-oxoguanine (8-oxoG) DNA glycosylase activity (Lovell et al., 2000) and POLβ expression levels (Weissman, et al., 2007a, 2007b) were found in different brain regions of AD brains compared to normal aged brains. For AD brains, the patients were found to carry OCG1 mutations, with different mutations leading to impaired 8-oxoG DNA glycosylase activity (Mao et al., 2007), altered PRP1 and XRCC1 interactions, reduced ability to bind substrates, and reduced AP lyase activity (Jacob et al., 2013).

PARP1, a key protein for SSB recognition, has also been found to be functionally impaired in AD brains and mouse models. In the CA3 region of the adult rat brain, Aβ can activate PARP1 by increasing oxidative stress (Strosznajder et al., 2000), and the introduction of exogenous NAD+ can alleviate Aβ-induced DNA damage (Wu et al., 2014)]. PARP1 can also promote AD disease development by affecting metabolism, and PARP1 activity has been found to be associated with elevated PAR levels in AD brains (Love et al., 1999; Strosznajder et al., 2012).

In 3xTg-AD mice, knocking down POLβ leads to neuronal death, memory loss and impaired synaptic plasticity accompanied by increased DNA damage (Sykora et al., 2015). Recent reports have also focused on the role of mitochondrial BER in AD (Canugovi et al., 2014; Santos et al., 2013).

Tau and DNA damage

Tau is a microtubule-associated protein encoded by *MAPT* (Houda Benhelli-Mokrani et al., 2018a, 2018b) and is thought to be localized in the cytoplasm. Tau was shown to react with nucleic acids and localize in the nucleus of neuronal cells (Brady et al., 1995; Bukar Maina et al., 2016; Frost et al., 2014; Greenwood & Johnson, 1995; Lu

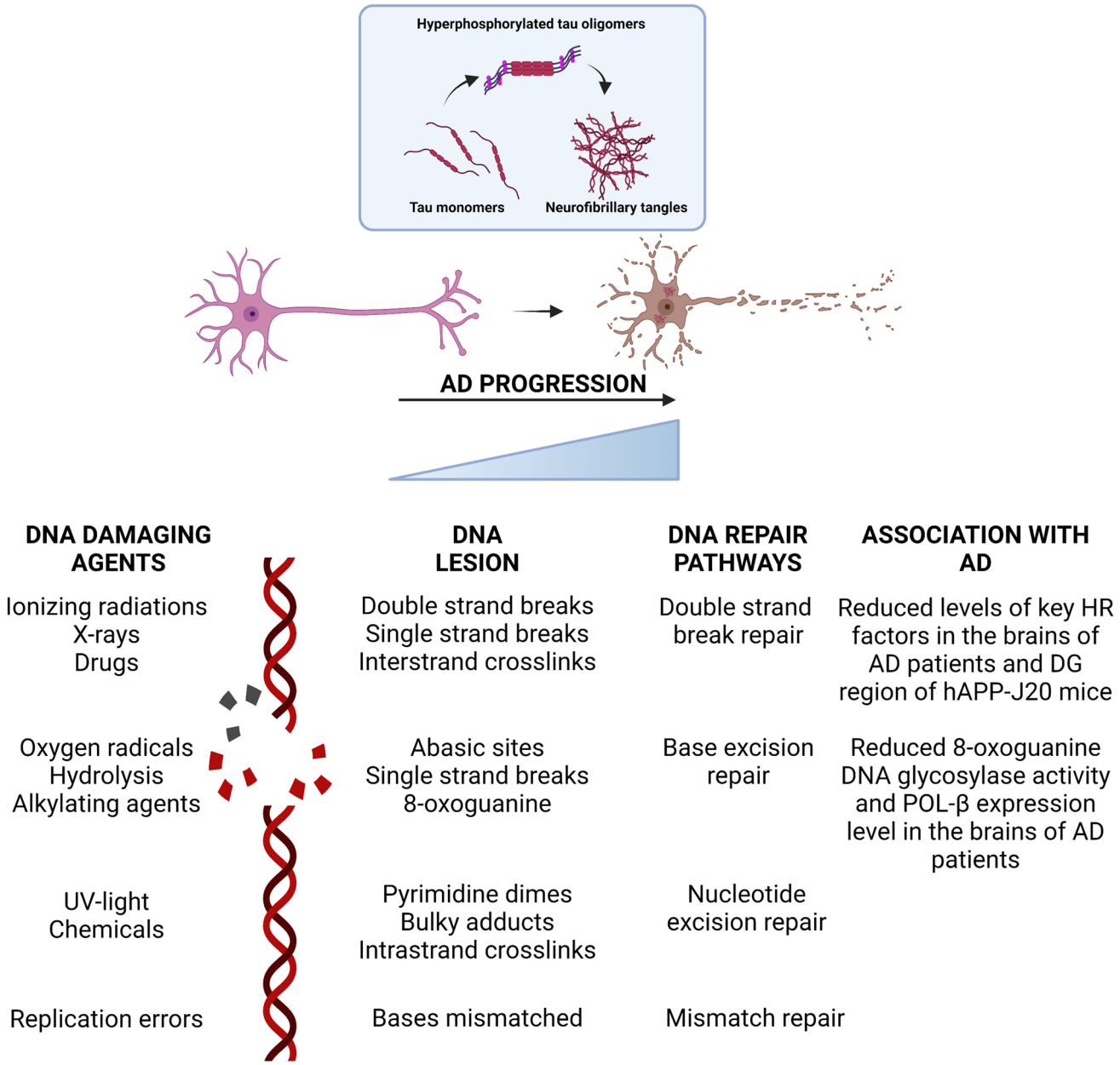

Fig. 1 DNA damage repair pathways and their potential relationship with AD

et al., 2014). In mouse primary neurons, tau can bind to chromatin, and this binding is dynamically variable and regulated by cellular stress (H. Benhelli-Mokrani et al., 2018a, 2018b). In addition, in primary neurons, Tau can participate in the DDR process, and in the absence of Tau, the level of γ-H2AX is elevated (Violet et al., 2014). Although the mechanism is not clear, these results suggest that Tau may facilitate the process of cellular DDR. A similar trend was found in the mouse brain, where both DNA DSBs and γ-H2AX were at higher levels and DNA repair processes were impaired in Tau knocked out mice (Violet et al., 2014). A shift in the localization of Tau to the nucleus along with a decrease in its phosphorylation level was also observed upon the induction of DNA damage in cells (Ulrich et al., 2018).

Tau oligomers may also affect DDR (Violet et al., 2015). In mouse models, the presence of Tau oligomers is accompanied by an increase in Polβ expression (Zheng et al., 2020). Tau multimers have also been reported to alter the localization of key proteins of the DDR pathway, such as BRCA1 and 53BP1 (Kurihara et al., 2019; Nakamura et al., 2020), but the exact mechanism is still unclear.

Conclusion

Here, we reviewed recent studies on DNA damage in age-related AD, which focused on DNA damage in AD and the impact of DDR on disease progression. Maintaining the integrity of the genome is crucial for the physiology of any nucleated cell. Oxidized DNA is believed to be the most common DNA lesion in neurons, which is unavoidable due to their high metabolic activity. Aside from oxidized DNA, a second major threat to neuronal genomes comes from DNA DSBs arising from the development and plasticity of the brain.

It is now increasingly clear that the DNA damage response plays an important role in the AD process. Mutations or deletions in core DDR proteins may accelerate the development of AD disease. On the other hand, the link between DDR and brain aging and neurodegenerative diseases remains complicated. Several similar results showed that oxidative DNA damage may originate from environmental neurotoxin threats (Migliore & Coppedè, 2009), may be associated with aging-related functional deficits (Coppedè & Migliore, 2010), or may be the result of neurodegeneration (Coppedè & Migliore, 2010; Taupin, 2011). DNA damage undoubtedly exacerbates the process of aging and neurodegenerative diseases; therefore, studies are necessary to explore the specific underlying mechanisms of damage and the repair involved (Fig. 1).

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