DNA Damage-Induced Neurodegeneration

Subjects: Neurosciences

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DNA repair ensures genomic stability to achieve healthy ageing, including cognitive maintenance. Mutations on genes encoding key DNA repair proteins can lead to diseases with accelerated ageing phenotypes. Some of these diseases are xeroderma pigmentosum group A (XPA, caused by mutation of XPA), Cockayne syndrome group A and group B (CSA, CSB, and are caused by mutations of CSA and CSB, respectively), ataxia-telangiectasia (A-T, caused by mutation of ATM), and Werner syndrome (WS, with most cases caused by mutations in WRN). Except for WS, a common trait of the aforementioned progerias is neurodegeneration. Evidence from studies using animal models and patient tissues suggests that the associated DNA repair deficiencies lead to depletion of cellular nicotinamide adenine dinucleotide (NAD+), resulting in impaired mitophagy, accumulation of damaged mitochondria, metabolic derailment, energy deprivation, and finally leading to neuronal dysfunction and loss. Intriguingly, these features are also observed in Alzheimer's disease (AD), the most common type of dementia affecting more than 50 million individuals worldwide. Further studies on the mechanisms of the DNA repair deficient premature ageing diseases will help to unveil the mystery of ageing and may provide novel therapeutic strategies for AD.

Keywords: DNA damage ; DNA repair ; Alzheimer’s disease (AD) ; age-related disease

1. An Overview of DNA Damage and DNA Damage Response (DDR)

1.1. DNA Damage and DDR

DNA carries genetic instructions for the development, functioning, growth, and reproduction of cells. DNA is inherently unstable due to both spontaneous chemical instability and modifications caused by either exogenous or endogenous agents causing DNA damage [1][2]. It has been estimated that each individual cell is subjected to up to one million DNA changes per day [3][4][5][6]. DNA damage is well known to affect both DNA replication, transcription, and a broad spectrum of signaling pathways including the nucleus to the mitochondria signaling pathway [1][7]. In this review, we update the progress of mechanistic studies on the key DNA repair pathways, including base excision repair (BER), nucleotide excision repair (NER), and double-strand break repair (DSBR). Furthermore, we focus on the role of DNA damage in ageing-related neurodegenerative diseases, with particular attention to its role in both rare premature ageing diseases, and the age-predisposed condition Alzheimer’s disease (AD).

Unlike other macromolecules of the cell, DNA cannot be replaced, but must be repaired to remain intact and functional. To avert deleterious consequences of DNA damage, cells have evolved several mechanisms, collectively termed the DNA damage response (DDR), to detect DNA damage, signal its presence and promote its repair. A variety of DDR pathways have been identified in organisms ranging from bacteria to humans, and are essential to life [8]. Three main repair pathways in mammalian neurons, including base excision repair (BER), nucleotide excision repair (NER), and double strand break repair (DSBR), are discussed below.

1.2. Major DNA Repair Pathways and Their Roles in Neurons and Microglia

BER (**Figure 1**) is the major pathway involved in the repair of oxidative lesions and is responsible for the repair of non-bulky DNA oxidation, deamination, and alkylation [9][10][11]. The first step in the BER pathway uses a lesion-specific DNA glycosylase to recognize and eliminate damaged base pairs, which initiates the pathway [12]. Either a bifunctional or monofunctional DNA glycosylase catalyzes the cleavage of the *N*-glycosidic bond by flipping the damaged base out of the double helix to release a free base and create an abasic site (AP site). The repair is further processed by AP endonuclease 1 (APE1) to cleave the DNA backbone 5′ to the AP site, hereby producing 3′-hydroxyl and 5′-2-deoxyribose-5′-phosphate (5′-dRP). The gap is then filled by DNA polymerases using 3′-hydroxyl through template-directed synthesis via either short-patch or long-patch repair, depending on the number of inserted nucleotides. In the case of short-patch BER, DNA polymerase β (Polβ) and the inherent dRP-lyase activity of Polβ detaches the 5′-dRP to replace a single nucleotide. In general, long-patch repair requires the assistance of Polδ/ε and flap endonuclease 1 (FEN1) to substitute

the displaced 5′-end structures with 2–13 nucleotides [10]. The importance of BER has been exemplified by the lethality of *Ape1*$^{-/-}$ or *Polβ*$^{-/-}$ mouse models. Deletion of mouse APE1 (also known as Apex1) leads to embryonic lethality, and deficiency in cells can promote cellular senescence and premature ageing features [13]. It has been demonstrated that Polβ defects can hamper amyloid β (Aβ)-induced neurogenesis in mice [14]. In particular, knockdown of Polβ inhibited the 42 amino acids form of Aβ peptide ($Aβ_{1–42}$)-promoted differentiation of nestin^{+} progenitor cells into nestin^{+}/Distal-less homeobox 2 (Dlx-2^{+}) neuroblasts [14]. Moreover, pharmacological blockage of Polβ prevented $Aβ_{1–42}$-induced differentiation of progenitors into MAP-2^{+} neurons [14]. It is worth noting that many proteins involved in BER not only exist in the nucleus, but also in the mitochondria [8]. Mitochondrial DNA (mtDNA) is more susceptible to the adverse effects of reactive oxygen species (ROS) produced during oxidative phosphorylation than nuclear DNA [15]. Thus, BER is considered to be the main repair pathway for DNA damage in mitochondria [16][17].

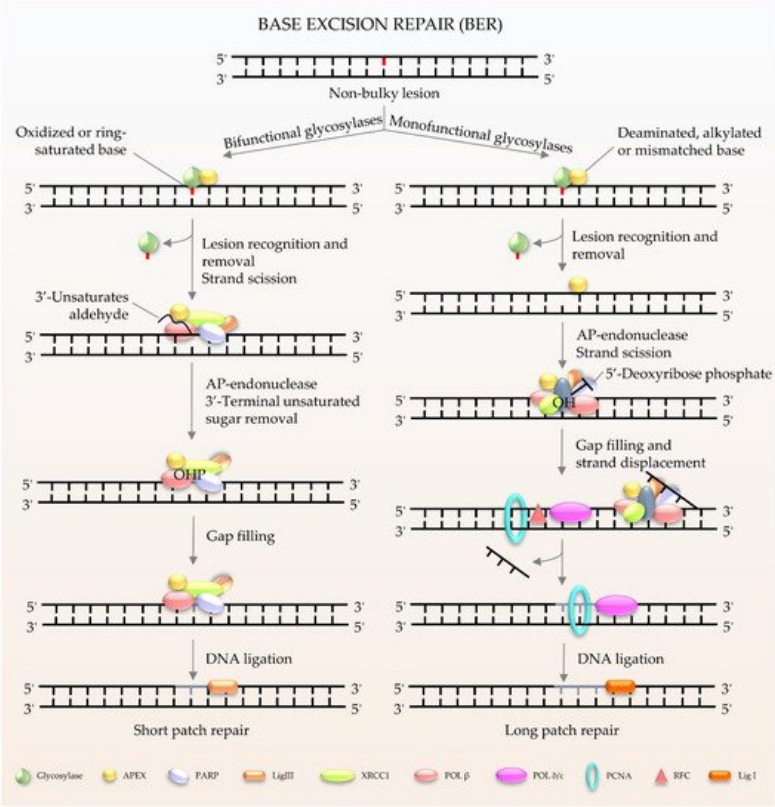

Figure 1. Schematic of BER in mammalian cells. BER is the key pathway to remove and repair damaged bases. It starts with a DNA glycosylase to recognize and eliminate the damaged base, creating an abasic site. The gap is finally filled by DNA polymerases. The short patch is repaired with a single nucleotide, and the long patch is synthesized with 2–13 nucleotides.

NER (**Figure 2**a) is a central DNA repair pathway and a highly dynamic process responsible for removing bulky lesions from the genome [18][19][20]. In humans, NER is composed of two branches, global genome NER (GG-NER) [21] and transcription-coupled NER (TC-NER) [22][23], which are distinguished by their different recognition methods. XPC, as the main damage recognition factor, scans the double helix to identify the lesion, and forms a complex with centrins, HR23B, etc., to induce GC-NER activity [24]. In the case of TC-NER, it is primed by transcribing RNA polymerase II [25]. After recognition, the two factors share the same pathway for repairing the damage. The repair factor XPA and the large multi-subunit transcription factor IIH (TFIIH) act as translocase and helicase, respectively, to unwind the DNA [19][26]. The DNA lesion is then excised through double DNA nicks with two endonucleases, XPF and XPG. Finally, the gap is filled by Polδ/ε and ligase I [21][22].

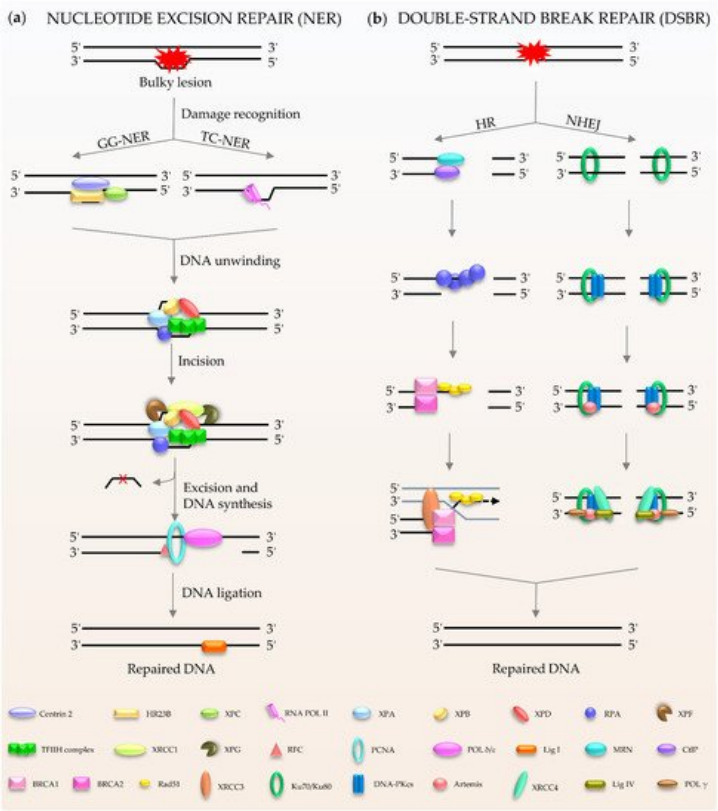

Figure 2. Schematic of NER and DSBR in mammalian cells. (**a**) NER is composed of GG-NER and TC-NER. XPC scans the double helix to identify the lesion, and forms a complex with centrins, HR23B among others, to induce NER activity. Subsequently XPA and TFIIH act as translocase and helicase to unwind the DNA. The DNA lesion is excised by XPF and XPG. Finally, the gap is filled by DNA polymerases and DNA ligase I. (**b**) DSBR consists HR and NHEJ. HR is initiated by MRN. Rad51 participates in the search for homologous copies, and its homologues are involved in DNA strand invasion and subsequent homologous recombination to repair. NHEJ is activated by Ku80/Ku70. The damaged ends are trimmed by artemis; after that, the gap is filled by the action of DNA polymerase. The final repair is mediated by DNA ligase IV and cofactor XRCC4.

Double-stranded breaks (DSBs) are the most harmful type of DNA damage in terms of genomic integrity [27]. Mammalian cells use two main DSBR pathways: homologous recombination (HR) and non-homologous DNA end joining (NHEJ) (**Figure 2**b) [28][29][30][31][32]. HR is the main method for DSBR utilized during embryogenesis and embryonic development [33]. The damaged ends of DNA are recognized by the Mre11-Rad50-Nbs1 (MRN) complex [34]. This complex performs extensive DNA processing, which together with CtIP generates 3′ single-stranded DNA (ssDNA). Rad51 participates in the search for homologous copies, and its homologues are involved in DNA strand invasion and subsequent HR to achieve highly accurate damage repair [35]. The cyclic heterodimer Ku70/Ku80 triggers NHEJ and then recruits DNA-PKcs [36][37][38][39]. Afterwards, nucleases (such as Artemis) deal with the damaged ends, and the gap is filled by DNA polymerases, such as Pol μ/λ/γ [40][41]. The final step of the repair pathway is mediated by DNA ligase IV and X-ray repair cross-complementing protein (XRCC4) [39][41]. It is well known that the process of DDR requires ATP, especially for DNA ligation. In humans, in response to DNA damage, cells mobilize more than ten thousand ATP molecules to repair just one DSB [42]. Interestingly, DNA ligase IV, the key enzyme of DSBR, uses NAD^+ as a substrate for double-strand connection to mediate the final repair [43].

Neuronal homeostasis is a prerequisite for the development and function of the nervous system, and requires high fidelity and stable inheritance [44]. In normal cellular activities or DNA replication, the high precision and integrity of the genome must be maintained after DNA damage. Multiple DDR pathways in cells drive the biological functions ensuring this procedure. During the early stages of neuronal development, that is, neural progenitor proliferation, the nervous system has entire DDR pathways. In other words, it can repair double-strand breaks through two pathways of HR and NHEJ before neuronal maturation (**Figure 3**) [11][44]. In contrast, during neuronal maturation, NHEJ becomes the only way to repair double-strand break damage [45]. Defects in these DDRs can cause neurological disorders. Studies have shown that defects in NHEJ, NER, or BER increase risks to neurodegenerative disorders or neurodevelopmental defects [46][47][48][49][50][51].

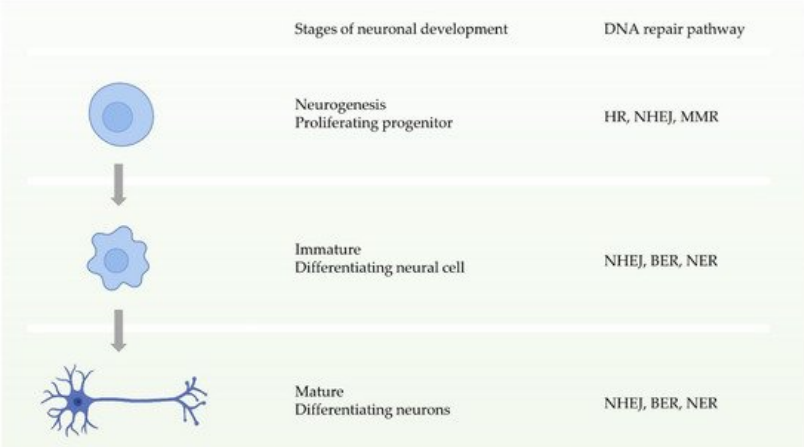

Figure 3. Schematic of the availability of different DNA repair pathways during different stages of neuronal development.

Microglia are glial cells widely distributed in the brain and spinal cord. They are the main form of active immune defense in the central nervous system, and are key cells involved in the neuroprotective functions that maintain normal brain function; however, microglia can be hostile to neurons in disease conditions [52][53]. Studies have shown that DDR-related proteins have an impact on the activity, function, and survival status of microglia. In DDR, especially in DSBR, the deficiency of one crucial protein, ataxia-telangiectasia mutated (ATM) [54], results in abnormally active microglia, and stimulates excessive production of pro-inflammatory factors, which result in neurotoxicity [55]. More specifically, ATM dysfunction causes damage to DNA repair, and leads to the further accumulation of impaired cytoplasmic DNA. In microglia, cytoplasmic DNA can subsequently activate an antiviral defense system via the DNA sensor stimulator of interferon genes (STING). Cytoplasmic DNA can also trigger absent in melanoma 2 (AIM2) inflammasomes and, in parallel, induce elevated levels of cytokine precursors, such as pro-IL-1, through proteolytic processing. These processes create an extreme environment of neurotoxic inflammation [55]. In addition, the DNA excision repair protein, ERCC1, is very important for NER and DSBR [56]. Loss of ERCC1 results in microglial death and a compensatory increase in proliferation [57]. Of note, it is speculated that, in a mouse model of *Cx3cr1-Ercc1*$^{ko/loxP}$ and *Cx3cr1-Ercc1*$^{wt/loxP}$, *Ercc1*-deficient microglia might have a link with ageing-related phenotypes [57].

2. Crosstalk between Nucleus and Mitochondria in DNA Damage

DNA damage not only accumulates in chromosomal DNA, but also in mtDNA, leading to mitochondrial dysfunction [58]. Dysfunctional mitochondria are targeted for lysosomal destruction through mitophagy and are recycled for cell utilization, as well as being degraded by the ubiquitin-proteasome system (UPS) [59]. Mitochondrial dysfunction and mitophagy defects are likely key features of age-related neurodegenerative disorders [60]. The accumulation of mtDNA damage and the reduction of mitophagy are also hallmarks of premature ageing diseases, such as XP and A-T [61][62][63]. Although organisms have a large number of responses to DNA damage, not only will DNA lesions increase during ageing, but the efficiency of DDR will also decrease [7][64][65][66][67]. Many accelerated ageing diseases, such as XP, A-T, CS, and WS, and neurodegenerative diseases such as AD, are closely related to the mutation of DDR proteins and DNA damage in both the nucleus and mitochondria [68][69][70][71][72].

Crosstalk between the nucleus and mitochondria is essential for cellular function [7][63]; this crosstalk is a response to different ‘stimulators’ such as oxidative stress, DNA damage, and mitochondrial dysfunction [73][74]. There are accurate and rigorous regulatory mechanisms between the two organelles to control the stability of mitochondria [74]. One of them is that the nucleus regulates mitochondrial function through the poly-ADP-ribose polymerase 1 (PARP1)–NAD^+–sirtuin 1 (SIRT1) signaling pathway (**Figure 4**). NAD^+ is an important substrate for enzymes like PARPs and the NAD^+-dependent deacetylases (sirtuins or SIRTs). NAD^+ plays a key role in DDR. PARP1 monitors DNA lesions and subsequently recruits DNA repair proteins through PARylation, while consuming NAD^+ [7][75]. PARP1 is continuously activated due to the accumulation of nuclear DNA damage. Hyperactivity of PARP1, as shown in multiple DNA repair deficient models (CS, XP), can lead to NAD^+ depletion, thereby reducing the activity of sirtuins, and finally leading to mitochondrial dysfunction via impaired mitochondrial biogenesis and depleted mitophagy [76]. The sirtuin family shuttles between the nucleus, mitochondria, and cytoplasm in response to cell stimulation [74][77][78][79][80]. In addition, studies have shown that mutation of the *C. elegans pme-1*, the homologue of mammalian *PARP1*, increased NAD^+ levels and Sir2.1 (the homologue of SIRT1 in *C. elegans*) activity, as well as increasing both healthspan and lifespan; mechanistically, this effect is at least partially contributed to by increased mitochondrial homeostasis through UPR^{mt} activation [63][68][81]. PARP1 interacts with SIRT1 to achieve signal transduction from the nucleus to the mitochondria [7]. Further studies on the role of PARP1–NAD^+–SIRT1 signaling in nucleus-mitochondria crosstalk are necessary.

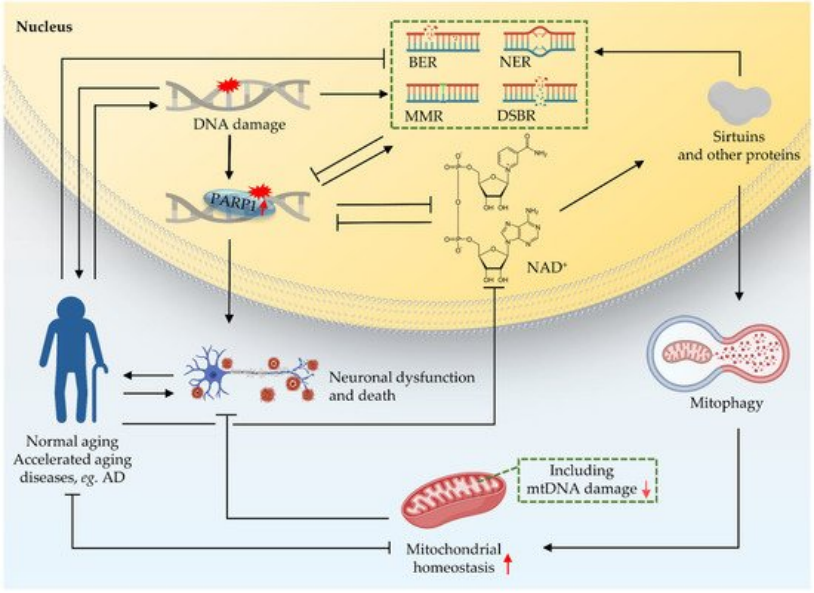

Figure 4. Crosstalk between nucleus and mitochondria in premature ageing and AD. Nuclear DNA damage can lead to mitochondrial dysfunction. One of the pathways through which the nucleus regulates mitochondrial function is the PARP1–NAD^+–SIRT1 signaling pathway. NAD^+ plays an important role as a reaction substrate in various pathways of DDR. Together, these contribute to ageing and the neurodegeneration in accelerated ageing. Black arrows indicate promotion, and inverted T bars indicate repression. Red arrows indicate up- or downregulation.

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