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Chromatin regulation of DNA damage repair and genome integrity in the central nervous system

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Abstract

With the continued extension of lifespan, aging and age related diseases have become a major medical challenge to our society. Aging is accompanied by changes in multiple systems. Among these, the aging process in the central nervous system is critically important but very poorly understood. Neurons, as post-mitotic cells, are devoid of replicative associated aging processes, such as senescence and telomere shortening. However, because of the inability to self-replenish, neurons have to withstand challenge from numerous stressors over their lifetime. Many of these stressors can lead to damage of the neurons' DNA. When the accumulation of DNA damage exceeds a neuron's capacity for repair, or when there are deficiencies in DNA repair machinery, genome instability can manifest. The increased mutation load associated with genome instability can lead to neuronal dysfunction and ultimately to neuron degeneration. In this review, we first briefly introduce the sources and types of DNA damage and the relevant repair pathways in nervous system (summarized in Figure 1). We then discuss the chromatin regulation of these processes and summarize our understanding of the contribution of genomic instability to neurodegenerative diseases.

DNA damage and repair in the central nervous system

DNA is constantly faces attack from both exogenous and endogenous sources. The most common environmental related DNA damage is caused by excessive exposure to sunlight (UV radiation) and tobacco smoke, which primarily affect skin and lung cells, respectively. Protected by the skull, spine and the blood-brain/spinal cord-barrier, the central nervous system is guarded from most exogenous sources of DNA damage, but remains vulnerable to ionizing radiation, including X-rays and cosmic rays, and certain chemotherapeutic reagents

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that penetrate these barriers. This is typically manifested as DNA strand breaks, which must be efficiently repaired to maintain genome integrity.

Primarily due to the brain's high demand for energy, the endogenous sources, such as the metabolic products, are responsible for most of the DNA damage that occurs in the brain [1]. It is estimated that about 20% of the oxygen and 25% of the glucose that are consumed by our body are devoted to brain functions [2]. Mitochondria use this oxygen and glucose to generate ATP primarily through oxidative phosphorylation. The by products of this reaction, reactive oxygen species (ROS), and their reaction products, such as reactive nitrogen species (RNS) and lipid peroxidation products, are very harmful to DNA. The most common lesions created by these metabolism products include apurinic/apyrimidinic (AP) sites (abasic sites), oxidized base, such as 7,8-dihydro-8-oxoguanine (8-oxoG) and 8-hydroxy-2-deoxyguanosine (OHdG), and single stranded breaks (SSBs). It is also possible that one form of lesion can be turned into another form. For example, AP sites, if not repaired, can be converted to SSBs. The estimated number of DNA lesions caused by endogenous sources is in the range of 10^4 to 10^5 per cell per day [3, 4].

To preserve genomic integrity, there are at least four active DNA repair pathways in nervous system [1, 5], each corresponding to particular types of DNA lesions (Figure 1). In each case the DNA damage must be detected, the lesion removed or the ends processed, the gaps filled and ligated and the chromatin state returned to the pre-lesion state. Base excision repair (BER) mechanisms correct DNA base modifications such as those produced by ROS. Nucleotide excision repair (NER) pathways remove helix distorting lesions and cross-links caused by UV radiation and chemical agents. There are two sub-pathways of mammalian NER: global genome nucleotide excision repair (GG-NER) and transcription-coupled nucleotide excision repair (TC-NER), which differ in the initial detection step. GG-NER repairs general helix distorting lesions anywhere in the genome, while TC-NER recognizes DNA damage that blocks RNA polymerase II. Additionally, single strand break repair (SSBR) and double strand break repair (DSBR) pathways mend DNA strand breaks caused by ionizing irradiation or chemotherapy reagents. Importantly, SSBs are also intermediate products of BER, thus there is significant overlap between SSBR and BER pathways. Double-strand breaks are repaired through one of two mechanisms: nonhomologous end joining (NHEJ) or homologous recombination (HR) repair. HR is the major pathway used during S/G2 phase, where the broken DNA is repaired using sister chromatid as template. NHEJ repair can happen during any phase of cell cycle and it is the primary means for repairing DSBs in post-mitotic neurons. Because the damaged DNA terminals need to be processed before rejoining, errors can be introduced during NHEJ repair.

Failure to properly repair damaged DNA can result in mutations that have dire consequences on cell function. Mis-repaired DNA in actively transcribed regions can cause altered expression or function of the corresponding proteins. Some transcription blocking lesions can even directly lead to cell death. Such mutagenesis in dividing cells can impose substantial risk for developing cancer in some cases; however, in the post-mitotic cells of the nervous system, it mostly results in milder cellular dysfunction, possibly culminating in neurodegeneration.

In addition to permanent alteration of potentially important DNA sequences, the DNA damage response is a very energy consuming process that can in and of itself perturb cellular function if over-activated. For instance, as described in next section, in response to DSB, histone H2A.X is phosphorylated, and this phosphorylation spreads in both directions surrounding the damage site for at least megabase of chromatin. It is estimated that 10^4 ATP molecules are necessary to repair a single DSB [3]. Similarly, PARP1 (Poly(ADP-ribose) polymerase-1) activation during the DNA damage response can lead to nicotinamide adenine dinucleotide (NAD^+) depletion, which can in turn disrupt the functions of NAD^+ dependent enzymes (such as Sirtuins) and/or promote cell death through mitochondrial release of apoptosis-inducing factor (AIF) [6]. Thus, energy starvation resulting from deregulated DNA damage responses (DDRs) can also perturb neuronal function and ultimately contribute to neurodegeneration.

In addition to nuclear DNA (nDNA), mitochondrial DNA (mtDNA) is also subject to endogenous and exogenous damages. In fact, the mutation rate of mtDNA is at least 10 fold greater than that of nDNA [7]. Recent studies show that, although the chromatin regulation of DNA repair is absent due to the lack of histones, the major repair pathways are preserved in mitochondria. Readers are referred to these excellent reviews addressing mtDNA integrity and its link to aging and neurodegeneration [8, 9].

DNA damage repair in the chromatin context

DNA is organized into nucleosome core particles, where 147 bp of DNA wraps in 1.67 left-handed superhelical turns around a histone octamer. The histone octamer is composed of H3-H4 tetramer flanked by two H2A-H2B dimers. Their exposed histone tails are enriched with post-translational modifications. The nucleosome core particles are connected through linker DNA to form the structure of "beads on a string". The chromatin can also be further packed into 30nm fibers or higher level with linker histone (H1) and other scaffold proteins depending on the nuclear context. These various types of chromatin packing must be highly regulated during gene expression to allow the transcription machinery access to DNA. Likewise, chromatin modification is essential for DNA repair proteins to reach sites of DNA damage, though chromatin modifiers also play more active roles in DNA damage signaling.

Researchers appreciated as far back as the 1990's that chromatin modifications were likely to play important roles in DNA damage repair. An "access-repair-restore" model was initially proposed for NER [10] and was later extended to DSB [11]. In this model, the compact organization of chromatin is thought to act as a barrier for efficient DNA repair. Thus, chromatin decondensation is necessary to allow the repair machinery to access DNA damage sites, and the original nucleosome-DNA structure must be restored after repair. Accordingly, multiple histone remodeling proteins and histone modifying factors that help to open up chromatin structure to allow initial signaling of DNA damage have been identified. At the same time, evidence has accumulated showing that chromatin modifiers can play more active roles in DNA damage repair. Histone variants and histone modifications can function to organize and stabilize DNA repair machinery. Chromatin structure can also help to restrain DNA damage signaling and suppress transcription in the vicinity of the damage

site. A revised "prime-repair-restore" model emphasizes these positive players and considers the whole process a more concerted effort [10, 12].

Certain types of repair, such as DSB repair through the HR pathway (which requires searching for a homologous template), or NER repair of distorted double helices, are likely to require significant chromatin remodeling and modification. And indeed, we gained most of our knowledge about chromatin remodeling from the studies of DSB and NER pathways. It has become increasingly clear that these processes involve at least 4 distinct mechanisms of chromatin remodeling: 1. Histone chaperones that regulate histone deposition, exchange, etc.[13]; 2. Histone variants that are differentially incorporated into chromatin in different cellular context. For example, the incorporation and modifications of H2A variants H2A.X and H2A.Z are dynamically regulated at DNA damage sites and play important roles in DNA damage repair [12]; 3. Histone post-translational modifications; 4. ATP-dependent chromatin remodeling. In this review, we will focus on histone modifications and ATP-dependent chromatin remodeling in mammalian systems. Although most of the current literature is based on non-neuronal systems, a number of recent studies have shown the conservation of these mechanisms in the central nervous system; we will pay special attention to those in the following section. It is also important to note that there is extensive functional crosstalk among all of these mechanisms in the processes of DNA damage detection, repair and restoration. For instances, histone modifiers and chromatin remodelers frequently form complexes and act in the concerted way, i.e. histone deacetylases HDAC1 and/or HDAC2 and chromatin remodeler CHD3 or CHD4 together form the NuRD complex. Similarly, specific histone variants or histone modifications usually associate with designate histone chaperons [12, 14].

Histone post-translational modifications are important ways of regulating DNA accessibility, chromatin dynamics and the binding of non-histone proteins. Most modifications occur in the N-terminal extensions of histones (histone tails), including but not limit to serine and threonine phosphorylation, lysine acetylation, lysine and arginine methylation, ubiquitination, sumoylation and poly-ADP-ribosylation.

1) Poly-ADP-ribosylation (PARylation) and PARP1

Poly(ADP-ribose) polymerase-1 (PARP-1) is an ubiquitous nuclear protein that transfers ADP-ribose from NAD^+ to protein acceptors. It contains zinc fingers mediating DNA binding and a BRCT (BRCA1 [breast cancer 1] C terminus) motif for interaction with other DNA repair proteins [15]. PARP1 is thought to act as a sensor that binds to DNA strand breaks and is activated to catalyze the assembly of poly(ADP-ribose) (PAR) chains onto histones and other protein substrates including itself. PARP1 facilitates DNA repair by attracting PAR interacting factors and inducing chromatin relaxation [16–20]. In addition, PARP1 recruits macroH2A (an H2A variant), which binds to PAR and mediates chromatin looping and compaction [21]. Furthermore, since PAR is a bulky, negatively charged adduct, its attachment often changes protein properties and interferes with nucleosome/DNA interactions. Besides its important roles in the DDR, PARP overactivation can lead to cell death due to NAD^+ and ATP depletion [22, 23]. Therefore, PARP1 activity and the assembly/disassembly of PAR and PAR interacting proteins at the DNA damage sites need

to be tightly regulated to ensure both efficient DNA repair and proper cellular function [24, 25].

2) Acetylation/deacetylation

Hyperacetylation of histone following UV radiation is one of the first identified chromatin modifications associated with DNA damage [26]. Acetylation of histone H4 and H2A by the histone acetyltransferase (HAT) Tip60/KAT5 promotes an open chromatin structure and the recruitment of repair proteins [27, 28]. In particular, acetylation of histone H4 on lysine 16 (ac H4K16) is known to induce decondensation of compact chromatin fibers [29, 30]. Moreover, acetylation of histone H3 on Lys56 (ac H3K56) is believed to promote nucleosome reassembly following DNA repair or DNA synthesis [14]. Consistently, HATs catalyzing these modifications, including MOF/MYST1, Tip60 and CBP/P300 (CREB [cAMP response element binding protein] binding protein), are known to play pivotal roles in DNA repair [14, 27, 31, 32].

Histone deacetylation was long thought to only participate at the late stages of DNA repair to restore chromatin structures. Recently though, several studies have revealed underappreciated roles of histone deacetylases (HDACs), the enzymes remove acetyl groups from lysine residues on histones, in early phases of DNA repair, and their roles are particularly relevant to neurodegeneration [33–37]. In neurons, the NAD^+-dependent deacetylase Sirtuin 1 (SIRT1) is required not only for efficient DNA damage repair, but also for initial DNA damage signaling [34]. SIRT1 is recruited to DSB sites within seconds of damage and its deletion leads to the diminished phosphorylation of both H2A.X (Ser139) and ATM (ataxia telangiectasia mutated, on Ser1981), both early markers of DNA damage. Interestingly, SIRT1 deacetylates HDAC1, which also plays important roles in DNA repair, to stimulate its enzymatic activity. Consistently, increased acetylation of HDAC1 at Lys432 is found in two mouse models of neurodegeneration that exhibit increased DNA damage. In addition to HDAC1, DSB repair protein NBS1 is also deacetylated by SIRT1 in response to DNA damage.

Deacetylation of H3K56 is an early event in the DDR, whereas the H3K56 re-acetylation is usually observed hours after DNA damage, concomitantly with chromatin reassembly [38]. SIRT6, HDAC1 and HDAC2 are all able to deacetylate H3K56 [33, 37]. Interestingly, in parallel with H3K56 deacetylation, SIRT6 also simultaneously promotes the binding of ATP-dependent chromatin remodeler SNF2H to nucleosomes [37]. Although ATM phosphorylation (Ser1981) is not disrupted in the absence of SIRT6, the recruitment of downstream factors, including γH2A.X, 53BP1 (p53-binding protein 1), RPA (replication protein A) and BRCA1, are significantly impaired. Importantly, SIRT6 plays a direct role in maintaining genome integrity in the central nervous system. The reduced chromatin association of SNF2H, H3K56 hyperacetylation and DNA damage accumulation are all detected in the brain of SIRT6 KO mice [37, 39]. In addition to its deacetylase activity, SIRT6 also acts as a mono-ADP ribosyltransferase that activates PARP1 to promote BER repair [40, 41].

Like H3K56, acetylation of H4K16 (acH4K16) also shows a biphasic response in borh non-neuronal and neuronal cells [33, 34],. Its deacetylation at DNA damage sites has a similar

fast kinetics, however the renewal of acH4K16 occurs around 2 hours after DNA damage, while it takes more than 6 hours for re-acetylation of H3K56 [33], indicating an active involvement of acH4K16 in the repair step of DDR [32]. HDAC1 and HDAC2 are responsible for deacetylating H4K16 at DNA damage sites [33]. The rapid deacetylation of H4K16 may regulate DNA damage repair in several ways. First, it has been shown to facilitate 53BP1 binding to the DSBs and promote NHEJ repair [42]. Second, as we increasingly appreciate the balance and coordination among various cellular processes, H4K16 deacetylation may help setting boundaries by condensing chromatin adjacent to DNA damage sites, which would not only prevent the uncontrolled expansion of repair proteins and excessive processing of DNA ends, but also inhibit local transcription from unrepaired DNA template [43, 44]. All of these remains to be proven in the nervous system.

Knock-down of both HDAC1 and HDAC2 in tumor cell lines results in greater defects in NHEJ repair compared to HR [33]. However, in central nervous system, HDAC1 seems to play a dominant role in DSB repair. HDAC1, but not HDAC2, directly interacts with both SIRT1 and FUS (Fused in sarcoma), two upstream factors of the DDR. SIRT1 deacetylates HDAC1 and stimulates its activity (see above). FUS mutations are linked to familial amyotrophic lateral sclerosis (fALS) and disease associated mutations are enriched in the HDAC1 interacting domains of the FUS protein. Several of the most frequently identified FUS mutants are defective in recruiting HDAC1 in response to DNA damage. Concomitantly, these FUS mutations also result in DNA repair deficits *in vitro*, and accumulated DNA damage in the motor cortex of fALS patients [45].

3) Phosphorylation, ubiquitination and methylation

The phosphorylation of H2A.X at Ser139 (γH2A.X) is one of the best-studied DSB induced histone modifications [46]. Three PI-3 kinases, ATM, ATR (ataxia telangiectasia and Rad3-related) and DNAPK (DNA-dependent protein kinase), are known to be capable of phosphorylating H2A.X [47–49]. γH2A.X appears immediately following DSB, and spreads at least a megabase of chromatin in both directions adjacent to DSB sites [50, 51]. γH2A.X serves as a center to organize the repair machinery and coordinate the DDR with other cellular functions such as cell cycle arrest [52].

Histone ubiquitination is found following both UV induced DNA damage and DNA DSB and can increase the accessibility of chromatin. For example, polyubiquitination of H2A by the E3 ligases RNF8 (RING finger protein 8) and RNF168 facilitates the binding of downstream factors, such as BRCA1, 53BP1 [53–56]. Similarly, H2B ubiquitination by RNF20 is required for recruitment of SNF2H [57].

Proper histone methylation is also important for DNA damage repair. For example, trimethylated histone H3 on lysine 9 (H3K9me3) at DSBs is required to activate the acetyltransferase activity of Tip60 and to successfully repair DSBs [58]. Likewise, the recruitment of 53BP1 to DNA damage sites depends on its interaction with dimethylated histone H4 on lysine 20 (H4K20me2) [59].

ATP-dependent chromatin remodelers are usually multi-subunit protein complexes that use the energy of ATP hydrolysis to alter DNA-nucleosome interactions. They can slide,

exchange or evict histone H2A-H2B dimers or whole histone octamers. They all contain an ancient SWI2/SNF2 ATPase subunit and based on the identity of this subunit, they are categorized into 4 major families named after their founding members: SWI/SNF (SWItch/ Sucrose Non-Fermentable), ISWI (Imitation SWI), INO80 (INOsitol requiring) and CHD (CHromodomain helicase DNA-binding) [60]. Other uncategorized ATPase remodelers include ERCC6-CSB complex, ATRX (Alpha Thalassemia/mental Retardation syndrome X-linked) and RAD54L [61–65]. Members of each group are important for DDR pathways.

Mammalian SWI/SNF ATPases BRG1 and BRM stimulate efficient NER repair and DSB repair. They both have C- terminal bromodomains that mediate interactions with acetylated histones. Their recruitment to the damage sites is part of the activation loop of the DDR and helps facilitate functional factor recruitment, phosphorylation of H2A.X and histone acetylation [66–68]. Similarly, both ATPases of the ISWI family complexes, SNF2H and SNF2L, are recruited to DNA damage sites, with SNF2H recruitment dependent on SIRT6 and H2B ubiquitination by RNF20 [37] [57]. The exact role of these ISWI family members in the DDR remains unclear, however, their reduced expression renders cells hypersensitive to DNA damage indicating they do play an important role in the repair process [69, 70].

The mammalian INO80 complex functions in the early stage of NER repair by facilitating the assembly of NER factors at the damage sites [71]. Recently, the yeast INO80 complex has also been shown to promote global chromatin mobility upon DNA DSB, which could facilitate the search for homologous DNA templates required for HR [72]. Another INO80 family member, p400, is recruited as part of NuA4 HAT complex through the interactions with γH2A.X. p400 is able to substitute H2A-H2B dimers with H2A.Z-H2B dimers. H2A.Z exchange at DSBs is required for acetylation of histone H4 by Tip60, another subunit of NuA4 complex. These two actions together create an open and relaxed chromatin microenvironment adjacent to DSB, which in turn promotes the ubiquitination of histones and the loading of multiple proteins important for NHEJ and HR [73, 74].

CHD family proteins all contain tandem chromodomains N-terminal to their ATPase domains. Among them, CHD3 and CHD4, two different catalytic subunits of the NuRD (NUcleosome Remodeling Deacetylase) complex, have been directly implicated in DNA repair. Interestingly though, NuRD complexes containing CHD3 versus CHD4 appear to play very different roles in DDR. CHD3 interacts with SUMO1 (Small Ubiquitin-like MOdifier 1) modified TRIM28 (TRIpartite Motif containing 28; also known as KAP-1), a key component of heterochromatin, through its C-terminal SUMO-interacting motif. Upon DNA damage, ATM phosphorylates KAP-1 at Ser824 promoting dissociation of CHD3 and concomitant chromatin relaxation [75]. This release of CHD3 from heterochromatin is required for efficient DSB repair. In contrast, CHD4 has been found to play a positive role in DSB repair. CHD4 is quickly recruited to DSB sites by RNF8, an ubiquitin ligase, to promote chromatin decondensation. This recruitment facilitates the assembly of RNF168 and BRCA1 at the break sites and the further ubiquitination of H2A, which together amplify the DDR signal [76, 77]. In addition, the recruitment of CHD4 containing NuRD complex is also partially dependent on the enzymatic activity of PARP [17, 18]. In the latter case, CHD4 is thought to block transcription close to DNA damage sites and to support repair and cell survival by regulating p53 deacetylation.

Another CHD family chromatin-remodeling enzyme, ALC1 (Amplified in Liver Cancer 1, also known as CHD1L), is also recruited to DNA damage sites through a PARP1 dependent mechanism. PAR binding activates ALC1 which can then catalyze nucleosome sliding [19, 78]. Either depletion or overexpression of ALC1 results in sensitivity to DNA-damaging agents. Moreover, ALC1 is recruited and functions through similar mechanism in (UV)-induced NER repair [20].

Is genome instability a general contributor to neurodegeneration?

Early studies on a number of neurodegenerative disorders revealed a hypersensitivity of non-neuronal cells derived from Xeroderma Pigmentosum, Cockayne Syndrome, Huntington's disease, Alzheimer's disease and Parkinson's disease patients to DNA damaging agents [79–85]. These observations strongly suggest that these cells are either more prone to DNA damage, or that their DNA repair pathways are compromised. Further, the finding that even non-neuronal cells from these patients had compromised ability to deal with DNA damage suggests the presence of intrinsic defects in these cells. That is, their DNA damage sensitivity is not likely a secondary consequence of neurodegeneration. These studies were conducted before the genetics of any of these diseases was understood; more recent research using genetic models of such disorders has found evidence of increased DNA damage in the CNS in many cases [34, 45, 86]. Similarly, postmortem studies of human brain tissue also demonstrate increased DNA damage in these disorders [45, 87, 88]. Thus, there is often a strong correlation between neurodegeneration and DNA damage sensitivity and/or DNA repair deficits. While a causative role for DNA repair defects in the most common neurodegenerative diseases remains to be established, a number of rare disorders clearly demonstrate that perturbation of DNA repair pathways can lead to neurodegeneration.

Genome instability can lead to neurodegeneration: Lessons from genetic diseases

The best evidence supporting a causal role for DNA repair deficiency in neurodegeneration comes from the studies of a number of rare genetic diseases. Patients with mutations in NER molecules develop Xeroderma Pigmentosum, Trichothiodystrophy or Cockayne Syndrome, which share common clinical features, including UV sensitivity and progressive neurodegeneration [89–91]. Two specific form of ataxia, Ataxia with Occulomotor Apraxia-1 (AOA1) and Spinocerebellar Ataxia with Axonal Neuropathy (SCAN1) are linked to mutations in APTX (aprataxin) and TDP1 (tyrosyl-DNA phosphodiesterase 1) respectively [92–94], both molecules involved in SSBR. In contrast, mutations in key molecules of DSBR are usually associated with human syndromes characterized by microcephaly, such as ATR-Seckel Syndrome, Nijmegen Breakage Syndrome, LIG4 (LIGase IV, DNA, ATP dependent) Syndrome and XLF (XRCC4 [X-ray Repair Cross Complementing protein 4]-Like Factor, also known as nonhomologous end joining factor 1) Syndrome, indicating the importance of DSBR pathway during neurogenesis [95, 96]. However, Ataxia Telangiectasia (A-T) and A-T Like Disease (ATLD) are the exceptions [97, 98]. The exact mechanisms for this discrepancy remain elusive.

DNA damage, cell cycle re-entry and copy number variations

It has been well established that cell cycle activity is abnormally upregulated in the early stage of AD progression by the re-expression of a number of cell cycle regulators, such as PCNA, Cyclin B1, Cyclin D, Ki-67, p16, CDK4 and others [99–101]. As noted above, there is also evidence that DNA damage is increased in AD patients [102]. Interestingly, there seems to be a reciprocal relationship between cell cycle activation and genome instability. On one hand, DNA damage is able to initiate cell cycle progression [103]. On the other hand, this aberrant cell cycle activity leads to partial or full DNA replication in normally post-mitotic neurons which ultimately triggers cell death [101, 103]. Such relationships and their contributions to neurodegeneration are corroborated in an inducible p25 overexpression mouse model, although the cause and effect relationships remain unclear [104]. p25 is a regulatory binding subunit of Cyclin-dependent kinase 5 (Cdk5), that is upregulated in various neurodegenerative conditions [105]. When it is overexpressed in forebrain excitatory neurons, the transgenic mice recapitulate several characteristics of AD, such as neuronal death, glial activation, amyloid beta elevation, tau hyperphosphorylation and aggregation, as well as cognitive decline [106, 107]. Importantly, in this mouse model, genes involved in cell cycle regulation and the DNA damage response are upregulated. Moreover, abnormal cell cycle activity and DSBs are simultaneously detected in hippocampal neurons at an early stage before any other disease-associated phenotypes can be detected. It was further demonstrated that reduced HDAC1 activity contributes to the effect of p25 on DNA damage and cell cycle alterations. Interestingly, HDAC1 overexpression can rescue neurons from DNA damage and ischemia associated cell death [104], suggesting that HDAC1 activation could provide therapeutic benefit for at least certain aspects of AD pathology.

A possible consequence of aberrant cell cycle activity and/or defective DNA damage repair is the production and/or propagation of copy number variations (CNVs) within the genome. Recent advances in sequencing technologies make single cell whole genome sequencing possible, allowing for the discovery of such small, low frequency deletions and duplications. In addition, developing induced pluripotent stem cell (iPSC) technologies allow us to monitor the same cell colony at different developmental stages. Using these techniques, significantly elevated numbers of CNVs have been found in both iPSC derived and postmortem neurons compared to fibroblasts or neural progenitors [108], indicating that post-mitotic neurons may be particularly prone to these types of mutations. Interestingly, 41% of postmortem neurons carry at least 1 CNV, whereas 15% of neurons account for the majority of all CNV calls, indicating that a subset of neurons have highly altered genomes. Also surprisingly, more deletion than duplication events are found, a feature only observed in neurons but not in fibroblasts or neural progenitors [108]. It remains to be determined whether these CNVs contribute to genome rearrangement, altered epigenetic landscape and neuron degeneration [109] as well as whether the degree of chromosomal alteration is associated with aging and degenerative status.

Stalled Transcription, R-loops and genome instability

The relationship between transcription and DNA damage is both intimate and intricate. In the aging human brain, there is a significant reduction in expression of genes responsible for neuronal functions. This reduction is concomitant with the increased oxidative DNA damage

in the promoters of down-regulated genes, which may interfere with binding of transcription factors [110]. If a DNA lesion occurs in the transcribed region, it may cause persistent stalling of RNA polymerase II and activate p53 dependent apoptosis. Moreover, transcription itself can introduce genome instability through R-loop (RNA/DNA hybrids) formation. In most cases, R-loops are formed when nascent RNA invades the DNA duplex during transcription. This nascent RNA can replace the un-transcribed strand of DNA and recombine into the genome. Since RNA is much more prone to breakage than DNA, R-loops are frequently processed to SSBs or DSBs [111]. Important evidence suggesting such a mechanism may play a role in neurodegeneration comes from the study of senataxin (SETX), the causal gene of AOA2 (ataxia with oculomotor apraxia type 2) and ALS4 (amyotrophic lateral sclerosis 4). SETX is an RNA/DNA helicase that protects genome integrity by resolving R-loops and promoting pause site-dependent transcriptional termination [112–114].

DNA molecules are subject to torsional strain during both transcription and replication, which must be relieved to prevent DNA damage. Type 1 and type 2 topoisomerases (TOP1 and TOP2) relieve such physical stress on the DNA by generating, and then repairing, single or double strand breaks, respectively. Despite the importance of these molecules, abortive topoisomerase activity, where the topoisomerase molecule becomes covalently linked to the DNA strand, can sometimes occur. Stalled topoisomerase I (TOP1)-DNA complexes are a common type of SSBs, which are normally removed by tyrosyl-DNA phosphodiesterase 1 (TDP1, the causal gene of SCAN1). It has also been shown that camptothecin, a TOP1 inhibitor, is able to generate DSBs and induce apoptosis in a transcription dependent manner. This effect could be rescued by RNase H1, which cleaves RNA/DNA hybrid [115, 116]. These results suggest that SSBs produced by the TOP1-cleavage complex can be processed to DSB when they interfere with transcription. In addition to TOP1, TOP2 is also active in neurons and its abortive activity leads to TOP2-linked DSBs. Tyrosyl DNA phosphodiesterase-2 (TDP2) is able to repair this type of DSB via NHEJ in an error-free manner [117]. Recently, homozygous mutations of the *TDP2* gene were identified as a potential cause of intellectual disability, epilepsy and ataxia in affected individuals. Hypersensitivity to TOP2-induced DSBs is observed in both lymphoblastoid cells from affected individuals and neural cells cultured from *Tdp2* mutant mice. Moreover, there is reduced transcription of genes important for the development and function of nervous system in *Tdp2* mutant mice, together with a 25–30% reduction in the density of interneurons in the molecular layer of the cerebellum of these mice. Collectively, these results suggest TDP2, like TDP1, play an important role in neurodegeneration.

Recently, the synthesis of small RNAs has also been shown to play a positive role in DNA damage repair. Two independent groups reported that DICER dependent 21–23 nucleotide RNAs are produced from sequences adjacent to DSB sites and are required for efficient DSBR [118, 119]. It is speculated that these small RNAs may function as guide molecules to recruit chromatin modifying factors and other signaling proteins to DSBs. Moreover, several RNA binding proteins, including FUS and RBMX, are rapidly recruited to DSBs in PARP-1 dependent manner and act as positive regulators of DSBR [45, 120–122]. It remains unknown, however, if their RNA binding ability is involved in the DNA damage repair process.

Neuronal activity, beta amyloid and DSBs

A recent study highlights the particular relevance of DSBR in the central nervous system. It was shown that physical activities such as learning and exploration induce transient DSBs in neurons that are readily repaired within 24 hrs. In contrast, DSBs are increased at baseline in an AD mouse model overexpressing human amyloid precursor protein (hAPP), and they persist after exploratory activity [123]. DSB induction was dependent on neuronal activity in both wild type and hAPP overexpressing mice. These new findings link DSBs, the most severe form of DNA damage, to physiological neuronal activity. They also suggest that AD mutations or pathologies can lead to persistent DSBs, which could in turn contribute to neurodegeneration. It appears important to study the physiological role of these transient DSBs in neurons as well as how they are produced and repaired. Similarly, understanding the mechanisms that contribute to persistent DNA damage in AD models could also provide insights into AD pathology.

DNA damage repair and trinucleotide repeat instability in neurological diseases

Several neurological diseases are caused by the expanded trinucleotide repeats in or close to a transcribed gene. For example, the expanded CAG repeats within the *HTT* (Huntingtin) gene lead to Huntington's disease (HD) [124] and the CGG repeat expansion within the *FMR1* (Fragile X Mental Retardation 1) gene is the cause of fragile X syndrome [125, 126]. Interestingly, although the trinucleotide expansion occurs in germ cells and is inheritable, its instability and mosaicism are also observed in non-dividing somatic cells including neurons [127].

Interestingly, evidence suggests that trinucleotide expansion could be a byproduct of BER or TC-NER. Loss of 7,8-dihydro-8-oxoguanine-DNA glycosylase (OGG1), a BER enzyme, suppresses age-dependent CAG expansion in the brains of HD mice [128]. Similarly, knockdown of CSB (Cockayne syndrome group B), a specific TC-NER protein, in human cells stabilizes CAG repeat tracts [129, 130]. Several proteins in the mismatch repair (MMR) pathway, which normally repairs insertions, deletions or mis-incorporated bases during DNA replication, are also involved in the trinucleotide repeat expansions [131–135]. The requirement of MMR proteins for repeat expansion in post-mitotic cells may involve a non-canonical MMR pathway, although the exact mechanism is currently not clear [136].

Metabolic and environmental regulation of DNA repair

Metabolic and environmental factors can also impact upon chromatin regulators and DNA damage repair pathways. For instance, Sirtuins and PARP1, which play important roles in DNA repair as outlined above, each require NAD^+ for their functions. Similarly, the co-factor acetyl-CoA (acetyl coenzyme A) is required for HAT activity, while SAM (S-Adenosyl methionine) is required for methyltransferase reactions. Thus, alterations in the levels of NAD^+, Acetyl-CoA or SAM have the potential to affect DNA repair pathways. Importantly, production of these molecules can be modulated by numerous nutritional and environmental factors, as well as by aging and in neurodegenerative disorders. A thorough review of the links between DNA repair and metabolism are beyond the scope of this manuscript but the reader is referred to recent reviews on the topic [137, 138].

Mutations that do not directly affect DNA repair proteins likely also impinge on DNA repair processes in neurodegeneration. For example, the well-characterized Parkinson's disease proteins Parkin, PINK1 (PTEN-induced putative kinase 1), and DJ-1 are all required for proper mitochondrial health and function [139]. The metabolic alterations and oxidative stress caused by inefficient mitochondrial respiration not only directly cause DNA damage, but potentially also impair the repair mechanisms that would normally counteract it [137, 138]. Similarly, a number of environmental toxins that are thought to increase risk for PD do so by impairing mitochondrial function [140], likely impacting oxidative damage and DNA repair pathways.

Conclusions and perspectives

It is essential that neurons counteract the damaging effects of genome instability across their lifetimes to maintain viability and proper function. A model emerges whereby levels of DNA damage and/or alterations in DNA repair can tip the scales between life and death for a neuron. Importantly, both damage and repair can be affected by perturbations in neuronal metabolic pathways, toxins or other environmental factors, or by genetic factors that directly affect DNA repair proteins or the pathways that regulate them. Chromatin modifiers play important roles in promoting DNA repair, and also provide a key link to metabolic and environmental cues. Furthermore, metabolic and DNA damage repair pathways are affected by aging, the greatest risk factor for neurodegeneration. While a causative role for increased DNA damage and genome instability in the most prevalent neurodegenerative diseases has not been established, rare genetic disorders such as Cockayne Syndrome and Ataxia Telangiectasia clearly show that a primary defect in DNA repair processes can result in a neurodegenerative phenotype. As such, it appears very likely that perturbations in DNA repair pathways, arising in any number of ways, do contribute to the pathology of common neurodegenerative disorders such as AD, PD, HD and ALS.

With the help of recent technological advances, particularly new sequencing technologies, iPSC techniques, high resolution imaging and tools for genetic manipulation, we will be able to answer many unresolved questions related to DNA repair in post-mitotic neurons. Among these will be a more thorough understanding of the chromatin regulation of these processes and how environmental and metabolic factors can modulate them. Importantly, a number of chromatin modifying enzymes have already been proven to be viable drug targets (i.e. Ezh1, Dot1). As such, targeting chromatin mechanisms could provide a means to correct DNA repair deficiencies, which could in turn provide valuable therapeutic benefit for neurodegenerative disease.

List of Abbreviations

DDR   DNA damage response

NHEJ   nonhomologous end joining

HR   homologous recombination

BER   base excision repair

NER	nucleotide excision repair
GG-NER	global genome NER
TC-NER	transcription coupled NER
SSBs	single strand breaks
DSBs	double strand breaks
PAR	poly- (ADP-ribose)
PARP1	poly- (ADP-ribose) polymerase-1
HAT	histone acetyltransferase
HDAC	histone deacetylase
ROS	reactive oxygen species
RNS	reactive nitrogen species
NAD	nicotinamide adenine dinucleotide
BRCT	BRCA1 [breast cancer 1] C terminus
53BP1	p53-binding protein 1
RPA	replication protein A
ATM	ataxia telangiectasia mutated
ATR	ataxia telangiectasia and Rad3-related
DNAPK	DNA-dependent protein kinase
TOP1	topoisomerase I
TDP1	tyrosyl-DNA phosphodiesterase 1
TDP2	tyrosyl-DNA phosphodiesterase 2
XLF	(XRCC4 [X-ray Repair Cross Complementing protein 4]-Like Factor
ATRX	Alpha Thalassemia/mental Retardation syndrome X-linked
OGG1	7,8-dihydro-8-oxoguanine-DNA glycosylases
FMR1	Fragile X Mental Retardation 1
MMR	mismatch repair
CNVs	copy number variations
iPSC	induced pluripotent stem cell
A-T	ataxia telangiectasia

ATLD	A-T like disease
NBS	Nijmegen breakage syndrome
AOA1	ataxia with occulomotor apraxia-1
AOA2	ataxia with occulomotor apraxia-2
SCAN1	-spinocerebellar ataxia with axonal neuropathy
HD	Huntington's disease
AD	Alzheimer's Disease
PD	Parkinson's disease
ALS	amyotrophic lateral sclerosis
fALS	familial Amyotrophic lateral sclerosis

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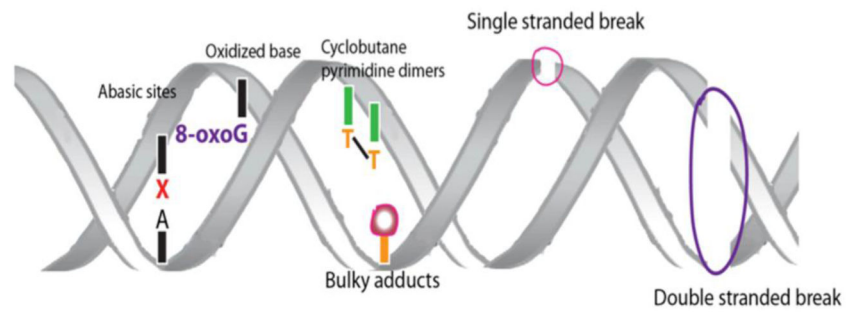
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highlights

- Neurons have to withstand challenge from numerous stressors that can lead to DNA damage

- The increased mutation load associates with genome instability, leads to neuronal dysfunction and ultimately to neuron degeneration

- Introducing the sources and types of DNA damage and repair pathways in nervous system

- Discussing the chromatin regulation of these processes

- Understanding the contribution of genomic instability to neurodegenerative diseases

Figure 1.
DNA damage and repair in central nervous system