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Review

DNA damage in neurodegenerative diseases

Fabio Coppedè*, Lucia Migliore**

Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy

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ABSTRACT

Following the observation of increased oxidative DNA damage in nuclear and mitochondrial DNA extracted from post-mortem brain regions of patients affected by neurodegenerative diseases, the last years of the previous century and the first decade of the present one have been largely dedicated to the search of markers of DNA damage in neuronal samples and peripheral tissues of patients in early, intermediate or late stages of neurodegeneration. Those studies allowed to demonstrate that oxidative DNA damage is one of the earliest detectable events in neurodegeneration, but also revealed cytogenetic damage in neurodegenerative conditions, such as for example a tendency towards chromosome 21 malsegregation in Alzheimer's disease. As it happens for many neurodegenerative risk factors the question of whether DNA damage is cause or consequence of the neurodegenerative process is still open, and probably both is true. The research interest in markers of oxidative stress was shifted, in recent years, towards the search of epigenetic biomarkers of neurodegenerative disorders, following the accumulating evidence of a substantial contribution of epigenetic mechanisms to learning, memory processes, behavioural disorders and neurodegeneration. Increasing evidence is however linking DNA damage and repair with epigenetic phenomena, thereby opening the way to a very attractive and timely research topic in neurodegenerative diseases. We will address those issues in the context of Alzheimer's disease, Parkinson's disease, and Amyotrophic Lateral Sclerosis, which represent three of the most common neurodegenerative pathologies in humans.

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* Corresponding author at: Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Medical School, Via Roma 55, 56126 Pisa, Italy. Tel.: +39 050 2218544.
** Corresponding author at: Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Medical School, Via Roma 55, 56126 Pisa, Italy. Tel.: +39 050 2218549.
E-mail addresses: fabio.coppede@med.unipi.it (F. Coppedè), lucia.migliore@med.unipi.it (L. Migliore).

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1. Introduction

The term neurodegenerative diseases describes a range of hereditary and sporadic conditions which are characterized by progressive nervous system dysfunction resulting from the degeneration of selected neurons in the human brain or spinal cord. As neurons deteriorate, an individual may first experience relatively mild symptoms such as problems with coordination or remembering names. However, with the increasing number of neurons that die, the symptoms get progressively worse, and many of these diseases are fatal. Some of the more well known neurodegenerative disorders include Alzheimer's disease (AD), Parkinson's disease (PD), and Amyotrophic Lateral Sclerosis (ALS) also referred to as motor neuron disease (MND) or Lou Gehrig's disease [1]. DNA damage, mainly in the form of oxidative DNA damage and cytogenetic damage, has been largely documented in clinical and preclinical stages of AD brains and peripheral tissues, and is believed to contribute to the neurodegenerative process [2]. Mitochondrial dysfunction and mitochondrial DNA (mtDNA) damage is well documented in PD, and several of the genes causing familial forms of the disease code either for mitochondrial proteins or proteins that are associated with mitochondria, all involved in pathways that elicit oxidative stress or free radical damage [3]. In addition, oxidative DNA damage has been hypothesized to contribute to motor-neuron degeneration in ALS [4]. As it happens for many neurodegenerative risk factors the question of whether DNA damage is cause or consequence of the neurodegenerative process is still open, and probably both is true. Indeed, DNA damage can accumulate in developing brain or spinal cord neurons during early life as a consequence of genetic predisposition, environmental exposure or epigenetic phenomena, leading to the origin of neuronal sub-populations characterized by mutation, copy number variation, or altered expression of certain genes, acting as foci of the neurodegenerative process later in life [5]. DNA damage can also accumulate in post-mitotic differentiated neurons as a consequence of ageing and/or environmental exposures to neurotoxicants, coupled with the age-related reduction of cellular antioxidant defences and DNA repair capabilities, and contribute to the selective degeneration of damaged neurons [6]. However, an increased DNA damage can also partially result from the oxidative damage and the reduced capability to repair it caused by the neurodegenerative process itself, or as a consequence of the cell-cycle re-entry and enhanced neurogenesis put in place to counteract neuronal damage and loss [7]. The accumulating evidence of global epigenetic changes in neurodegenerative diseases suggests that also those mechanisms could contribute to impaired DNA repair and chromosome damage in those disorders [8]. We will address those issues in the context of AD, PD and ALS, that represent three of the most common and studied multi-factorial neurodegenerative diseases.

2. DNA damage in Alzheimer's disease

2.1. Alzheimer's disease

Alzheimer's disease is the most common neurodegenerative disorder and the primary form of dementia among older people. Dementia is a general term to describe a severe decline in mental ability which includes the loss of cognitive functioning such as thinking, remembering and reasoning, coupled with changes in behaviour and personality severe enough to interfere with daily life. It is estimated that almost 36 million people in the world have dementia, and that this number will increase up to 115 millions by 2050, only as a consequence of the global ageing of the population in both developed and developing countries [9]. Concerning AD, dementia ranges in severity with time following the progression of the neurodegenerative process that takes place in selected brain regions, including the temporal and the parietal lobe, and parts of the frontal cortex and cingulate gyrus. After a pre-dementia stage, often defined as amnestic mild cognitive impairment (MCI), dementia usually starts as a mild condition, with patients that easily repeat questions, have problems handling moneys, tend to get lost, and start to have some mood and personality changes. This is followed by a moderate form of the disease often characterized by problems in recognizing family and friends, ending up to the most severe stage, when patients depend completely on others for the performance of daily activities. Therefore, AD is known for placing a great burden on caregivers, which are usually the partner or close relatives, and unfortunately there is no cure to halt the progression of the disease, making it a serious health concern and one of the most costly diseases to the society [9].

Affected brain regions in AD are characterized by the occurrence of extracellular amyloid deposits which are called senile plaques (SP) and by the presence of intra-neuronal aggregates of hyperphosphorylated tau protein denoted as neurofibrillary tangles (NFT) [10]. The amyloid β (Aβ) peptide is the main component of SP, and results from the cleavage of its precursor, the amyloid precursor protein (APP). Mutations in *APP* and presenilin (*PSEN1* and *PSEN2*) genes alter APP production and/or processing and cause early-onset (<65 years) familial forms of the disease, overall accounting for less than 1% of the total AD cases [1]. According to the amyloid cascade hypothesis of AD, changes in APP and/or Aβ homeostasis foster the assembly of Aβ into progressively higher order structures, from dimers all the way up to the insoluble plaques that finally deposit in the brain, and these events are sufficient to initiate the pathological and clinical changes of the disease [11]. Most of AD (90–95%) are however sporadic forms, diagnosed in people over 65 years of age and likely resulting from complex interactions among genetic, epigenetic, environmental, and stochastic factors superimposed on the physiological decline of cognitive functions with age [1]. Genetic association studies and more recent genome-wide approaches (GWAS) allowed the

identification of over 20 susceptibility genes for the sporadic forms, involved in synapse function and/or endocytosis, immune response, lipid metabolism, or both immune response and lipid metabolism, and with potential effects on APP trafficking, Aβ clearance or in mediating tau toxicity [12]. Among non-genetic factors associated with AD, ageing and family history are the major risk factors, but there is also indication of a correlation between serious head injury and future risk of AD. Moreover, growing evidence links brain health to heart health, and factors such as high blood pressure, midlife obesity, stroke, and type 2 diabetes are increasingly suspected to contribute to the cognitive decline. By contrast, physical activity, social engagement, brain stimulation, and a healthy dietary pattern (a diet high in fruits and vegetables, low in red and processed meats, and favouring mono- and polyunsaturated fats over saturated fats) might help to reduce risk of cognitive impairment, AD, and other forms of dementia [13]. Increasing evidence also points to an epigenetic contribution of environmental factors in AD. For example, certain dietary regimens or environmental exposure have been linked to epigenetic changes of *APP* or *PSEN1* gene expression leading to AD-resembling pathologies in animal brains [14,15]. In addition, studies in post-mortem human brains revealed global changes of epigenetic marks, including DNA methylation and hydroxymethylation as well as histone tail modifications [16,17].

2.2. Oxidative damage to nucleic acids in Alzheimer's disease

AD patients exhibit extensive oxidative stress to all cellular macromolecules, being detected peripherally as well as associated with the vulnerable regions of the brain. A summary of those studies is provided in Table 1. In addition, oxidative stress events occur early in the course of the disease and prior to the formation of the pathology, supporting an important role of oxidative stress in disease pathogenesis [18]. The oxidative attack of DNA by reactive oxygen species (ROS) can lead to the generation of more than 20 oxidized base adducts, the most prominent being 8-hydroxyguanine (8-OHG). Because of this, 8-OHG has been the predominant marker of DNA oxidation evaluated by means of a variety of analytical techniques, ranging from immunoassays for the analysis of urine samples, comet assays for the analysis of DNA damage in blood cells, and high pressure liquid chromatography (HPLC) coupled with electrochemical detection (ECD) or mass spectrometry (MS), or gas chromatography (GC) coupled with MS, for the analysis of DNA isolated from tissue specimens [19]. As a consequence, depending on the applied technique, DNA samples have been digested to nucleosides and DNA damage was evaluated as levels of 8-hydroxy-2′-deoxyguanosine (8-OHdG), or hydrolyzed to individual bases to detect 8-OHG levels [19].

In 1994 Mecocci and coworkers [20] measured 8-OHdG levels in DNA isolated from three regions of the cerebral cortex and the cerebellum in 13 AD and 13 age-matched controls, observing a significant 3-fold increase in the amount of 8-OHdG in mitochondrial DNA (mtDNA) in the parietal cortex of AD patients compared with controls as well as a small but significant increase in oxidative damage to nuclear DNA (nDNA) in AD samples. Those data showed, for the first time, that there is increased oxidative DNA damage in AD, and the authors hypothesized that it may contribute to the neurodegenerative process [20]. Subsequent studies, performed at the end of the last century, confirmed increased oxidative DNA damage in AD brains [21,22]. Indeed, increased levels of 8-OHG, 8-hydroxyadenine, 5-hydroxycitosine, and 5-hydroxyuracile, were observed in several post-mortem AD brain regions compared to control brains [21,22]. It was then confirmed that mtDNA has higher levels of oxidized bases than nDNA, that guanine is the most vulnerable base to oxidative DNA damage, and that multiple oxidized bases are significantly higher in post-mortem frontal, parietal, and temporal lobes of AD brains than control brains, with the temporal lobe being the most damaged region [23].

In 2006, oxidative DNA damage to both nDNA and mtDNA was observed for the first time in brain regions of patients affected by mild cognitive impairment, an intermediate stage between the expected cognitive decline of normal ageing and the more serious decline of dementia [24]. More recently, increased levels of 8-OHG have been observed in sections of hippocampus/parahippocamapal gyri of patients with a preclinical stage of AD (PCAD), a condition in which subjects show no overt clinical manifestations of AD but demonstrate significant AD pathology at autopsy [25]. Moreover, the levels of multiple oxidative base adducts were quantified in nDNA and mtDNA from the superior and middle temporal gyri, inferior parietal lobule, and cerebellum of age-matched normal control subjects, patients with MCI, PCAD, late-stage AD, and non-AD neurological disorders (frontotemporal dementia and dementia with Lewy bodies), and resulted significantly elevated in MCI, PCAD, late-stage AD, and patients with non-AD neurological disorders compared to normal control subjects. Nucleic acid oxidation peaked early in disease progression and remained elevated, suggesting that it represents a general event in neurodegeneration [26].

In 1999 Nunomura and coworkers provided the first evidence of increased RNA oxidation in vulnerable neurons in AD [27]. Subsequently, it was shown that 30–70% of the mRNAs isolated from AD frontal cortices were oxidized while the abundance of oxidized mRNAs was low in age-matched normal controls [28]. RNA oxidation was also detected in early stages and preclinical stages of AD [25,29]. Recently, it was shown that beside its well known role in microtubule dynamics, protein tau is also a key nuclear player in the protection of neuronal genomic DNA integrity from ROS, and it was suggested that tau alterations lead to a loss of its nucleic acid safeguarding functions and participate in the accumulation of oxidative DNA and RNA damage observed in the AD brains [30].

Oxidative DNA damage has been frequently observed also in biological fluids and peripheral tissues of AD patients. Increased 8-OHdG levels were observed in the ventricular cerebrospinal fluid (CSF) of AD subjects [31], and in lymphocytes of AD patients, besides a significantly lower level of plasma antioxidants [32,33]. Markers of oxidative DNA damage were also observed in CSF, urines and leukocytes of patients with mixed AD/vascular dementia [34]. Increased oxidative DNA damage was observed in lymphocytes of AD patients by applying the modified version of the comet assay for the detection of oxidized purines and pyrimidines [35–37], and we demonstrated that it occurs early in disease pathogenesis as it was detectable even in leukocytes of MCI patients that showed increased levels of primary DNA damage and oxidized bases respect to controls [37]. Others observed increased 8-OHG levels in sporadic AD fibroblasts [38].

In addition to oxidative base modifications, ROS attack to the DNA can result in the formation of DNA strand breaks (DSBs). The first suggestion that DSBs could contribute to neurodegeneration in AD dates back to 1990 when Mullaart and coworkers [39] showed a 2-fold increase in DSBs in the brain in AD. Others confirmed increased levels of DSBs in AD brain nuerons and suggested that it could represent an early event likely contributing to the subsequent formation of neurofibrillary tangles [40]. More recently, studies in mice revealed that a transient increase in neuronal DSBs occurs as a result of physiological brain activity, such as exploration of a novel environment. However, mice transgenic for human APP, which simulate key aspects of AD, had increased neuronal DSBs than control mice at baseline and more severe and prolonged DSBs after exploration, suggesting that Aβ exacerbates DNA damage [41].

In parallel with observations of oxidative DNA damage in brain and peripheral tissues of demented and pre-demented patients, several investigators questioned whether or not this could result from impaired DNA repair capabilities, mainly focusing on the DNA

Table 1
Examples of DNA damage and related mutations observed in Alzheimer's disease.

Type of damage	Year/years	Main observations	References
Oxidative damage	1994	First evidence of oxidative DNA damage in both mtDNA and nDNA from AD brains	[20]
	1997–2005	Increased oxidative DNA damage to multiple bases in AD brains and confirmation that mtDNA has higher damage than nDNA and that guanine is the most vulnerable base to oxidative attack	[21–23]
	2006	Increased oxidative DNA damage in mtDNA and nDNA from MCI brains	[24]
	2011–2014	Increased oxidative DNA damage in mtDNA and nDNA from preclinical AD (PCAD) brains	[25,26]
	1999	First evidence of RNA oxidation in AD neurons	[27]
	2006–2011	Confirmation of RNA oxidation in preclinical, early and late stages AD brains	[25,28,29]
	1999	Increased 8-OHdG levels in the CSF of AD patients	[31]
	1998–2008	Increased oxidative DNA damage in lymphocytes of AD patients	[32–37]
	2005	Increased oxidative DNA damage in lymphocytes of MCI patients	[37]
	2012	Increased oxidative DNA damage in fibroblasts of AD patients	[38]
DNA strand breaks	1990–1999	Increased levels of DNA strand breaks in AD brain regions	[39,40]
Mitochondrial DNA (mtDNA) mutations	1994–2014	Evidence of mtDNA deletions in AD brains	[51,52]
DNA adducts	2002–2006	No evidence of increased HNE/guanosine adducts in AD brains	[53,54]
	2005	Increased levels of acrolein/guanosine adducts in AD hippocampal regions	[55]
Cytogenetic damage	1973–1983	Early studies suggesting cytogenetic damage in peripheral AD blood cells	[58–62]
	1997	Increased frequency of micronuclei in AD lymphocytes, mainly originating from chromosomal malsegregation events	[63]
	1999	Preferential occurrence of chromosome 21 malsegregation in AD lymphocytes	[64]
	1999–2001	Increased frequency of micronuclei in AD fibroblasts and evidence of chromosome 21 and 18 malsegregation	[65,66]
	2008	Evidence of increased frequency of trisomy for chromosomes 21 (1.5-fold) and 17 (1.2-fold) in AD buccal mucosa cells	[67]
	2009	10-fold increase of chromosome 21 aneuploidy in the cerebral cortex in AD	[68]
	2014	Increased (2-fold) aneuploidy for chromosome X in female AD hippocampus	[77]
Epigenetic-related damage	2004–2005	Evidence that impaired folate metabolism induces chromosome 21 malsegregation in mitotic cells	[86,87]
	2005–2009	Evidence suggesting a link between environmental induced hypermethylation and subsequent accumulation of oxidative damage in AD-related genes in animal models of AD	[82–84]
	2011–2012	Evidence that impaired folate metabolism and methylation potential induce epigenetic changes in genes relevant for Aβ production and repair of oxidative DNA damage in cell cultures and animal models of AD	[14,94]

Abbreviations: Aβ, amyloid β; AD, Alzheimer's disease; CSF, cerebrospinal fluid; HNE, hydroxynonenal; MCI, mild cognitive impairment; 8-OHdG, 8-hydroxy-2′-deoxyguanosine.

base-excision repair (BER) pathway which is the main intracellular pathway for the removal of oxidized bases from the DNA, and especially on the enzyme 8-oxoguanine DNA glycosylase (OGG1) that removes 8-OHG from the DNA, and the DNA polymerase beta (POLβ) [42–44]. We reviewed the literature in the field that overall reveals impaired BER activity in both AD and MCI brains [2]. Some authors have suggested that mutations or polymorphisms in DNA repair genes might impair DNA repair activity in AD brains, but the hypothesis was not confirmed by genetic association studies [45]. Other hypotheses suggest that DNA repair proteins might be inactivated by oxidative induced post-translational modifications or degradation, as well as by epigenetic mechanisms, and that different isoforms of the same repair protein might be involved in the progression from early to late stages of AD [5]. More recent studies were focused on mitochondrial BER activities in AD and MCI subjects [46]. Also in this case the accumulation of oxidative lesions is paralleled by the failure in BER machinery, and a recent study in mitochondrial lysates of AD patients revealed that the 5-hydroxyuracil incision and ligase activities are significantly lower in AD brains, whereas the uracil incision, abasic site cleavage, and deoxyribonucleotide triphosphate incorporation activities are normal in these samples [47].

2.3. Mitochondrial DNA mutations in Alzheimer's disease

The mtDNA encodes for subunits of the mitochondrial respiratory chain, as well as for mitochondrial ribosomal RNAs (rRNA) and transfer RNAs (tRNAs). Oxidative DNA damage to the neuronal mtDNA, if not properly repaired, can lead to the formation of several mutations, including deletions and base substitutions [48]. In 2004, Swerdlow and Khan proposed the "mitochondrial cascade hypothesis" for AD, suggesting that the gene-determined make-up of an individual's electron transport chain sets basal rates of ROS production, which determines the rate at which acquired mitochondrial damage accumulates. The accumulation of oxidative mtDNA damage in turn causes energy failure, increased oxidative stress and formation of amyloid beta, which in a vicious cycle reinforce mtDNA damage and oxidative stress ultimately leading to neuronal degeneration [49]. Despite the evidence of mitochondrial dysfunction in AD, no causative mutation in the mtDNA has been linked to AD, and results of studies evaluating the role of mtDNA polymorphisms or haplogroups as AD risk factors are controversial [48,50]. Similarly, mtDNA deletions are markers of oxidative damage and believed to result from aberrant repair of damaged DNA. Indeed, many studies performed during the past two decades have investigated the incidence of mtDNA deletions, such as the 4977 bp deletion, known as the "common deletion", in post-mortem brain tissues of late-onset AD patients compared with age-matched normal control subjects [51,52], suggesting that they are associated with the biochemical deficits observed in late onset AD, but a causal relationship has not been yet established directly [52].

2.4. Indirectly ROS induced DNA damage in Alzheimer's disease

ROS attack to polynsatured fatty acids in membrane phospholipids generates acrolein, malondialdehyde, and hydroxynonenal (HNE), all able to interact with the DNA leading to bulky aldehydic DNA adducts. As such, aldehydic DNA adducts are an indirect

consequence of oxidative damage and can then promote DNA–DNA and DNA–protein cross-linking. Two independent studies have failed to observe increased HNE/guanosine adducts in AD brain regions [53,54], whereas increased levels of acrolein/guanosine adducts were observed in nuclear DNA extracted from the hippocampus of AD patients as compared to age-matched controls [55]. Acrolein has been shown to inhibit the mitochondrial activity, could modulate tau phosphorylation through different pathways, and caused cell death on neuronal primary culture from hippocampus, overall suggesting that it could play a role in the pathophysiology of AD [56].

2.5. Cytogenetic damage in Alzheimer's disease

Lymphocytes and skin fibroblasts have been largely used as surrogate peripheral tissues to investigate damage to the genome in relation to neurodegenerative disorders [57], and studies suggesting cytogenetic damage in AD peripheral tissues, albeit originally conflicting, date back to 30–40 years ago [58–62]. The application of the cytokinesis block micronucleus (CBMN) assay allowed us to detect high levels of spontaneous micronucleated binucleated cells in peripheral blood lymphocytes of AD patients [63]. Micronuclei are biomarkers of either chromosome malsegregation or breakage and, after application of the fluorescent in situ hybridization (FISH) technique utilizing a pancentromeric DNA probe, we found that the majority of micronuclei in AD lymphocytes tended to be centromere positive, indicating whole chromosome malsegregation rather than breakage [63]. We also applied dual-colour FISH with differential labelled DNA probes to obtain information on spontaneous chromosome loss and gain frequencies for both chromosomes 13 and 21 observing that, compared to lymphocytes of healthy controls, AD lymphocytes had higher frequencies of chromosome loss for both chromosomes, but particularly for chromosome 21 [64]. Studies in fibroblasts from both sporadic and familial AD patients revealed an increase frequency of micronuclei [65] and increased incidence of aneuploidy involving both chromosome 18 and 21 when compared to controls [66]. The analysis of buccal mucosa cells revealed a significant 1.5-fold increase in trisomy 21 and a significant 1.2-fold increase in trisomy 17 in buccal cells of AD patients compared to matched controls [67]. In addition, a 10-fold increase of chromosome 21-specific aneuploidy (both hypoploidy and hyperploidy) was detected in the cerebral cortex of AD patients with respect to what observed in the cerebral cortex of healthy controls [68]. Those studies revealed that AD cells are monosomic or trisomic (i.e. aneuploid) for various chromosomes, suggesting a general chromosome malsegregation defect. Moreover, many of those aneuploid cells have three copies of chromosome 21, the same defect that characterizes all cells in Down syndrome (DS) patients, reinforcing the original hypothesis that chromosome aneuploidy, particularly for chromosome 21, could be one of the mechanisms underlying both AD and the dementia that occurs in DS patients, raised in 1991 by Huntington Potter [69]. According to Potter's hypothesis, by a process of chromosome malsegregation during cell division (either in normal mitotic cells, neuronal precursors, or neurons themselves), AD patients essentially become mosaic DS patients, and because of chromosome 21 encodes the *APP* gene, its over-expression would ultimately contribute to the neurodegenerative process [69].

Studies performed in the last years have confirmed that the brain is, in fact, a complex genetic mosaic of aneuploid and euploid cells [70]. The possible function of neural aneuploidy and mosaicism could include contributions to cellular diversity, cellular signalling, and diseases of the central nervous system [70]. Furthermore, it was shown that also the human developing brain has mosaic nature, being composed of euploid and aneuploid neural cells, with an average aneuploidy frequency of 1.25–1.45% per chromosome, and an overall percentage of aneuploidy tending to approach 30–35% [71]. In the context of neurodegeneration, a global aneuploidization of the brain was observed in ataxia telangiectasia (AT). Particularly, the degenerating cerebellum in AT was remarkably featured by a dramatic 5–20-fold increase of non-random DNA double-strand breaks and aneuploidy affecting chromosome 14 and, to a lesser extend, chromosomes 7 and X [72]. Concerning AD, in addition to the 10-fold increase in chromosome 21 aneuploidy observed in the cerebral cortex [68], a case of young-onset AD due to occult mosaicism for trisomy 21 (10%) in lymphocytes was reported in a patient with no previous diagnosis of DS and only minimal physical manifestations of DS, and 3 similar prior cases of young-onset dementia associated with mosaicism for trisomy 21 were described [73]. In addition, mothers of DS patients younger than 35 years at conception are often mosaic for trisomy 21 [74,75], are prone to chromosome malsegregation, and are at 5-fold increased risk of developing AD later in life [76].

Since post-mitotic cells mainly populate the human brain the question is what causes aneuploidy in those cells, and two main mechanisms have been proposed to answer this question [77]. On one hand, it is plausible that certain individuals are more prone than others to chromosome instability during mitosis, and that chromosome malsegregation occurring in the human developmental central nervous system is a source for aneuploid cells in postnatal brains. As a consequence, mosaicism would be acquired during early brain development and could represent a risk factor contributing to late onset AD [69,76]. On the other hand, neural stem cells reside in the adult central nervous system of mammals revealing that the adult brain has the potential for self-repair, and neurogenesis occurs in the adult brain and is enhanced in the AD brain, likely acting as a regenerative attempt to compensate for the neuronal loss [78]. However, it was proposed that neurogenesis is prone to errors (i.e. abortive cell cycle due to re-entering of quiescent neurons into the cell cycle and replication stress) and generates new neuronal cells that are aneuploid, thus contributing to the increased genomic instability observed in AD cortical regions [7,79]. Such generated aneuploidy for chromosomes carrying genes involved in AD, would further promote the pathological process of AD [7]. In this regard, it was shown that neurons with a more-than-diploid content of DNA are increased in preclinical stages of AD and are selectively affected by cell death during the progression of the disease, confirming that hyperploidy of neurons originating from a failure of neuronal differentiation is a critical pathogenetic event in AD [80]. Very recently, X chromosome aneuploidy was evaluated in 10 female AD as well as 10 age and sex matched female control postmortem brain samples, revealing that rate of X chromosome aneuploidy in neural cells of the hippocampus and cerebrum was approximately two times higher in AD than in controls. In addition, one AD sample demonstrated mosaic aneuploidy of chromosome X confined to the hippocampus affecting about 10% of the cells, suggesting a possible predisposition of females affected by low-level mosaic X chromosome aneuploidy to AD [77].

2.6. Epigenetics and DNA damage in Alzheimer's disease

The research interest in searching for markers of oxidative stress in neurodegeneration, that characterized the end of the last century and the first decade of the present one, was shifted towards the search of epigenetic biomarkers of neurodegenerative disorders, following the accumulating evidence of a substantial contribution of epigenetic mechanisms to learning and memory processes, as well as to behavioural disorders and neurodegeneration [81]. DNA methylation represents one of the most studied mechanisms for regulating gene expression, with promoter hyper-methylation resulting in gene silencing, and a model has been proposed linking early-life induced epigenetic modifications, oxidative DNA damage,

DNA repair, and AD [82]. The authors observed that environmental influences occurring during brain development of rats, such as exposure to the xenobiotic metal lead (Pb), resulted in hypomethylation of the promoters of AD related genes, such as *APP*, as well as in hyper-methylation of several other genes. This early life imprint was sustained and triggered later in life to increase the levels of Aβ production and deposition, and was paralleled by increased levels of cerebral 8-OHG in adult brains [83,84]. It was therefore suggested that conditions leading to early life hyper-methylation of certain genes could render those genes more susceptible to the accumulation of Aβ induced oxidative DNA damage, since their methylation would render them less accessible to DNA repair proteins [82].

Another way through which epigenetics could contribute to either DNA or chromosome damage in AD takes as a starting point the folate metabolic pathway, which is the intracellular pathway that provides one-carbon units for the build-up of DNA precursors required during DNA synthesis and repair, as well as for DNA methylation reactions [85]. Folate metabolism is often compromised in AD patients, which are characterized by decreased serum folate levels that foster hyperhomocysteinemia and aberrant DNA methylation potential (reduced availability of the methyl donor compound *S*-adenosylmethionine) in those patients [85]. By means of in vitro studies it was demonstrated that folate deficiency induces chromosome 21 malsegration in mitotic cells [86,87], and some polymorphisms of genes mediating folate metabolism were linked to an increased frequency of micronuclei in blood cells of their carriers [88–90], as well as to an increased maternal risk for chromosome 21 malsegregation during pregnancy [91–93]. It is therefore plausible that impairments in folate metabolism, occurring in AD patients, could contribute to altered methylation and segregation of chromosome 21 in their cells [85]. Similarly, it was observed that folate deprivation in rodents induced demethylation of the *PSEN1* gene, with subsequent increased Aβ production and accumulation in the brain leading to AD-like pathology [14]. It was also demonstrated that an impaired DNA methylation potential, such as that resulting from folate deficiency, not only induces epigenetic changes leading to increased Aβ production, but also leads to epigenetic modifications of the gene coding for the repair protein OGG1 resulting in increased oxidative DNA damage in microglial BV-2 cells [94]. Furthermore, hyperhomocysteinemia, which is often observed in AD patients as a result of impaired folate metabolism, fosters tau hyperphosphorylation and formation of neurofibrillary tangles [95], which in turn lead to neuronal stress and aberrant cell-cycle re-entry [96], thereby contributing to the accumulation of chromosome damage in the AD brain [7]. Taken overall, those studies revealed a link between folate metabolism, chromosome damage, DNA methylation, oxidation, and repair, which further requires to be investigated in AD.

3. DNA damage in Parkinson's disease

3.1. Parkinson's disease

Parkinson's disease is the second most common neurodegenerative disorder after AD, affecting 1–2% of the population over the age of 65 years and reaching a prevalence of almost 4% in people above 85 years of age. The disease results from a progressive and profound loss of neuromelanin containing dopaminergic neurons in the *substantia nigra* (SN) with the presence of eosinophilic, intracytoplasmic inclusions termed as Lewy bodies (LBs; containing aggregates of α-synuclein as well as other substances), and Lewy neurites in surviving neurons, and is clinically characterized by resting tremor, rigidity, bradykinesia, and postural instability often accompanied by non-motor symptoms such as autonomic insufficiency, cognitive impairment, and sleep disorders. Also in the case of PD, only some improvements of the symptoms are offered by current treatments based on levodopa and dopaminergic therapy, but no drug is currently available to halt the progression of the disease [97].

In most of the cases PD is sporadic, likely arising from a combination of polygenic inheritance, environmental exposures, and complex gene–environment interactions superimposed on slow and sustained neuronal dysfunction due to ageing, that we recently reviewed [98]. A familial history of the disease is seen in almost 20% of the cases, and in a minority of them the disease is inherited as a Mendelian trait. Studies in PD families have led to the identification of at least 18 PD loci (PARK1-18) and several genes for PARK loci have so far been proposed [99]. At least five of them have been confirmed to cause inherited forms of typical PD. Particularly, mutation of a-synuclein (*SNCA*) and leucine-rich repeat kinase 2 (*LRRK2*) genes cause autosomal dominant PD, while autosomal recessive forms of parkinsonism are caused by mutations in the parkin gene (*PARK2*), the phosphatase and tensin homologue-induced putative kinase 1 gene (*PINK1*), and the DJ-1 gene (*DJ-1*) [98]. Studies on familial recessive forms of the disease have highlighted a central role for mitochondrial damage, repair, and turnover in the pathophysiology of the disease, with parkin, DJ-1, and PINK1 participating in the same or in similar/overlapping mitochondrial pathways [3], and more recent studies suggest that also *LRRK2* mutations and Lewy body pathology are associated with mtDNA damage in PD [100,101]. Common *SNCA* and *LRRK2* polymorphisms are among the most replicated susceptibility factors for sporadic PD, alongside with those in glucocerebrosidase (*GBA*) and microtubule-associated protein tau (*MAPT*) genes, overall indicating that accumulation and degradation of misfolded proteins, the autophagy–lysosomal pathway, and mitochondrial dynamics, transport, repair, turnover and mitophagy, are central pathways in PD pathogenesis [98]. A role for mitochondrial dysfunction and oxidative DNA damage in PD pathogenesis is further highlighted by environmental factors such as the mitochondrial toxins 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), rotenone, paraquat and maneb, all linked to human PD [102]. As such, most of the evidence of DNA damage in PD regards mtDNA damage (Table 2).

3.2. Oxidative damage to nucleic acids in Parkinson's disease

In 1994, Sanchez-Ramos et al. [103] reported that the levels of 8-OHdG were differentially distributed in PD brains with the highest concentrations in caudate, putamen, SN, and cerebral cortex. Concentrations of 8-OHdG were also found to be significantly elevated in PD caudate and SN compared with control individuals [103]. Subsequently, the analysis of post-mortem brain samples from PD and controls for a wide range of modified DNA bases by using gas chromatography revealed that the most striking difference was a rise in 8-OHG in PD SN, while rises in other base oxidation/deamination products were not evident [104]. Additional studies in PD patients revealed that cytoplasmic 8-OHdG immunoreactivity was intense in neurons of the SN and present, to a lesser extent, in neurons of the nucleus raphe dorsalis and oculomotor nucleus, as well as occasionally in glia. Those results were consistent with both RNA and mtDNA oxidation in PD brains [105]. 8-OHdG and 8-OHG levels were also measured in the serum and CSF of PD patients, and resulted significantly higher in PD patients than in age-matched controls [106]. We determined peripheral markers of oxidative DNA damage in PD blood and cultured lymphocytes, observing that, compared to healthy controls, PD patients showed higher frequencies of DNA single strand breaks and oxidized purine bases [107]. Increased urinary 8-OHdG levels were observed in PD patients with respect to controls, and urinary 8-OHdG levels were higher in the early stages of the disease [108].

Table 2
Examples of DNA damage and related mutations observed in Parkinson's disease.

Type of damage	Year/years	Main observations	References
Oxidative damage	1994	First evidence of oxidative DNA damage in PD brains	[103]
	1997	Increased oxidative DNA damage in PD SN revealing that guanine is the most vulnerable base to oxidative attack	[104]
	1999	Evidence of increased oxidative DNA damage to mtDNA and RNA in PD brains	[105]
	2001	Increased oxidative DNA damage in blood cells of PD patients	[107]
	2002	Increased oxidative DNA damage in serum and CSF of PD patients	[106]
	2010	Increased urinary 8-OHdG levels correlated with early stages of PD	[108]
DNA strand breaks	2001	Increased levels of DNA strand breaks in blood cells of PD patients	[107]
	2006	Increased levels of DNA strand breaks in PD brains	[130]
Mitochondrial DNA (mtDNA) mutations	2006–2013	Evidence of mtDNA deletions in PD neurons	[117,119]
	2012	Evidence of increased mtDNA point mutations in early stages of PD	[121]
	2014	Evidence that abasic sites precede mtDNA mutations in SN dopaminergic neurons	[123]
DNA adducts	2011	Increased levels of depurinating oestrogen-DNA adducts revealed in urine samples of PD patients	[126]
Cytogenetic damage	2001–2002	Increased frequency of micronuclei in lymphocytes of untreated PD patients, mainly originating from chromosome breakage events	[107,127,128]
	2010	No evidence of increased frequency of micronuclei in lymphocytes of PD patients treated with levodopa	[129]
Epigenetic-related damage	2012–2014	Evidence suggesting that the mitochondrial damage exerted by mitochondrial toxins in PD might be partially mediated by epigenetic mechanisms	[131–134]

Abbreviations: CSF, cerebrospinal fluid; 8-OHdG, 8-hydroxy-2′-deoxyguanosine; PD, Parkinson's disease; SN, substantia nigra.

A significant increase in 8-OHG levels was shown in mtDNA in nigrostriatal dopaminergic neurons of PD patients paralleled by elevated expression of the DNA repair proteins MTH1 (the oxidized purine nucleoside triphosphatase human mutT homologue), OGG1, and the DNA glycosylase MUTYH (mutY Homolog) [109]. Several studies have then focussed on the nature and extent of impaired DNA repair in PD neurons. Collectively those studies have revealed that parkin promotes DNA repair and protects against oxidative DNA damage and that parkin, PINK1 and DJ-1 work in the same or overlapping pathways related to maintenance of mitochondrial functional integrity under conditions of oxidative stress, that MTH1 is increased in the SN of PD patients and protects from oxidative damage caused by MPTP exposure, that OGG1 is increased in the SN of PD patients and protects against several insults such as those induced by manganese, MPTP, or methamphetamine exposure, and that MUTYH is increased in mitochondria of PD patients as a consequence of mtDNA damage (Reviewed in [110]). In addition, the DNA polymerase gamma (POLG1) participates in mtDNA replication and repair, several *POLG1* mutations have been observed to co-segregate in families with parkinsonism [111,112], and *POLG1* polymorphisms have been associated with sporadic PD risk [113,114]. More recently it has been shown that Lewy body pathology is associated with mitochondrial DNA damage in PD [100], and that reduced levels of the mitochondrial protein TOM40, the main component of the preprotein translocase of the outer membrane of mitochondria, mediates mitochondrial dysfunction (increased mtDNA deletions and oxidative damage) induced by α-synuclein accumulation in PD brains [115]. Similarly, increased levels of mtDNA damage were observed in patients carrying *LRRK2* mutations [101], overall indicating that many of the causative or susceptibility PD genes are directly or indirectly involved in the maintenance of the integrity of the mtDNA.

3.3. Mitochondrial DNA mutations in Parkinson's disease

Following the first report of mitochondrial complex I deficiency in PD by Shapira and coworkers [116], and the subsequent accumulating evidence of oxidative mtDNA damage in PD neurons described in the previous paragraph, several investigators have hypothesized that oxidative DNA damage could result in the accumulation of either point mutations or deletions in the mtDNA. An accumulation of high levels of mtDNA deletions was observed in SN neurons with ageing and in PD, suggesting that they may contribute to mitochondrial dysfunction and neurodegeneration [117]. The analysis of the nature of those deletions led to the identification of 89 different mtDNA deletions in single SN neurons from controls, PD patients, and a patient with Parkinsonism due to multiple mtDNA deletions, but there was no difference in the types of mtDNA deletions detected in these neurons, suggesting that the mechanism leading to the formation of these deletions in those three distinct groups could be the same [118]. More recently, it was shown that the primary accumulation of mtDNA deletions within SN pars compacta dopaminergic neurons, at an extent similar to that observed in patients with PD, do not kill dopaminergic neurons but trigger neuroprotective compensatory mechanisms at a mitochondrial level that may account for the high pathogenic threshold of mtDNA deletions in these cells [119].

On the contrary, early studies in the field failed to observe an increase of somatic point mtDNA mutations in the SN of PD patients [120]. Subsequently, it was hypothesized that failure to find increases in mtDNA point mutations in PD might be due to the fact that neurons with high mutation levels degenerate and thus are absent in late stage PD tissues. Indeed, the analysis of early stage PD cases and of cases of incidental Lewy body disease (ILBD), which is thought to represent a pre-symptomatic PD stage, revealed for the first time that mtDNA mutation levels in SN neurons are significantly elevated in this group of early PD and ILBD cases [121]. We already discussed in the previous sections that the proteins that are reported to be related to familial PD, including PINK1, DJ-1, alpha-synuclein, LRRK2, and parkin, are either mitochondrial proteins or are associated with mitochondria, are involved in pathways that elicit oxidative stress or free radical damage, and their mutation has been linked to increased mtDNA damage [4]. Mitochondria are continually exposed to ROS and accumulate oxidative damage more rapidly than the rest of the cell. Therefore, PD has been suggested to be associated with mitochondrial dysfunction [122]. A recent study was performed in human postmortem brain tissue and in in vivo and in in vitro models of PD in order to reveal the nature of the DNA damage preceding mutations in mtDNA, and showed it to be apurinic/apyrimidinic (abasic) sites in SN dopaminergic neurons, but not in cortical neurons from postmortem PD specimens [123]. In addition, exposure of rats to rotenone revealed that mtDNA damage is detectable prior to any signs of degeneration, and is produced selectively in midbrain neurons under conditions

of mitochondrial impairment. The selective vulnerability of midbrain neurons to mtDNA damage was not due to differential effects of rotenone on complex I, since rotenone suppressed respiration equally in midbrain and cortical neurons, but to the fact that, in response to complex I inhibition, midbrain neurons produced more mitochondrial H_2O_2 than cortical neurons. The persistence of abasic sites also revealed an ineffective base excision repair response in PD [123].

3.4. Indirectly ROS induced DNA damage in Parkinson's disease

Oxidation of catecholamines may lead to the formation of o-semiquinones and o-quinones in catecholaminergic brain tissues, and these reactive molecules may form DNA or protein adducts. Early studies performed almost 20 years ago in cell cultures revealed that the formation of DNA adducts by dopamine may contribute to the development of certain neurodegenerative diseases such as PD [124]. More recently, it was observed that slightly acidic conditions render competitive the reaction of dopamine-quinones with DNA to form depurinating adducts, suggesting that formation of those adducts could contribute to PD [125]. Indeed, depurinating oestrogen–DNA adducts were higher in urine samples of PD patients than in controls [126].

3.5. Cytogenetic damage in Parkinson's disease

In 2001 we first reported an increased frequency of micronuclei in peripheral lymphocytes of PD patients with respect to healthy matched controls [107]. Compared with controls, patients with PD showed an increase in the incidence of spontaneous micronuclei, DNA single strand breaks, and oxidized purine bases [107,127]. Fluorescence in situ hybridization analysis revealed that the percentage of centromere negative-micronuclei was higher than that of centromere-positive ones, arguing in favour of chromosome breakage rather than malsegregation as the origin of them in untreated PD patients [127,128]. Others observed increased 8-OHdG levels in peripheral blood lymphocyte DNA extracted from PD patients chronically treated with levodopa (the precursor of dopamine commonly used in PD treatment) with respect to controls, but no difference in micronucleus frequency was observed between the two groups [129]. However, little is still known in PD brains. The analysis of genomic DNA isolated from eight brain regions (frontal, temporal, and occipital cortex, hippocampus, caudate/putamen, thalamus, cerebellum, and midbrain) from five neuropathologically confirmed cases of PD and six control brains showed that DNA from midbrain in PD accumulated significantly higher number of strand breaks than age-matched controls. Caudate nucleus/putamen, thalamus, and hippocampus also showed more DNA fragmentation compared to control brains. In addition, DNA conformation was altered with imprecise base stacking in midbrain, caudate nucleus/putamen, thalamus, and hippocampus in PD [130].

3.6. Epigenetics and DNA damage in Parkinson's disease

At best of our knowledge there is no direct evidence of epigenetic modifications in PD directly linked to increased oxidative DNA damage, however several investigators observed that inhibitors of histone deacetylase (HDAC) proteins, a class of proteins required for epigenetic modifications of histone tails, restored both cognitive and motor functions in PD animal models induced by either over-expressing α-synuclein or by mitochondrial toxins such as MPTP, paraquat, maneb and rotenone, suggesting that epigenetic mechanisms are likely to contribute to mitochondrial dysfunction in PD [131,132]. In addition, treatment with the DNA methyltransferase (DNMT) inhibitor 5-aza-2′-deoxycytidine was shown to sensitize paraquat toxic effects on PC12 cell by oxidative stress increment and mitochondrial deficit [133]. Furthermore, a recent genome-wide DNA methylation analysis in brain and blood samples from PD patients revealed that among the top genes showing altered methylation levels there are those coding for glutathione-*S*-transferases GSTP1, GSTP2, and GSTT1, often associated with increased PD risk following exposure to pesticides [134]. Overall, those studies point to plausible epigenetic mechanisms mediating mitochondrial dysfunction following exposure to herbicides and pesticides.

4. DNA damage in Amyotrophic Lateral Sclerosis

4.1. Amyotrophic Lateral Sclerosis

Amyotrophic Lateral Sclerosis is an adult onset neurodegenerative disorder characterized by the degeneration of motor neurons in the motor cortex, brainstem and spinal cord, resulting in progressive weakness and death. The typical age at onset is between 50 and 60 years, and the incidence of the disease is similar worldwide ranging from 1 to 2 new cases per 100,000 individuals every year. Most of ALS cases (75–80%) have a limb onset with symptoms starting in either the upper or lower limbs. The remaining ALS cases (20–25%) have bulbar onset with the first symptoms being often dysarthria or dysphagia. However, in both cases the course of the disease is inexorably progressive with most of the patients dying within 3–5 years of the onset, generally due to respiratory failure. As for AD and PD, in the absence of a curative therapy, the management of ALS remains focused on the control of symptoms [135].

The gene encoding for the cytosolic copper–zinc superoxide dismutase protein (*SOD1* gene) was the first identified ALS gene, accounting for autosomal dominant forms [136]. Superoxide dismutases are scavenger enzymes against free radicals mainly produced by mitochondrial respiration, and *SOD1* mutations account for approximately 20% of the familial forms. This has led to an intense investigation on the possible contribution of oxidative stress and mitochondrial damage to disease pathogenesis, and most of our knowledge on the pathogenesis of the disease derives from studies on *SOD1* transgenic mice [137]. To date at least 16 genes and loci have been associated with ALS [134]; among them, those accounting for a reasonable percentage of familial ALS (fALS) cases include the *TARDBP* gene coding for the 43-kDa TAR DNA binding protein (TDP-43) and the fused in sarcoma (*FUS*) gene, accounting for approximately 4–5% of fALS cases each, and coding for RNA/DNA binding proteins, involved in alternative splicing, transcriptional regulation, mRNA stabilization, RNA transport, and microRNA processing [138–140]. In September 2011, an ALS-causing GGGGCC hexanucleotide repeat expansion within the promoter or first intron of *C9ORF72* has been described and represents the most frequent familial ALS causative mutation to date, accounting for 20–40% of the total ALS cases [141,142]. The mechanisms by which *C9ORF72* causes ALS are not yet fully elucidated, and the hexanucleotide repeat expansion is also found in frontotemporal dementia cases, as well as in sporadic ALS (sALS) cases [135,143]. If mutations of *SOD1*, *FUS*, *TARDBP*, and *C9ORF72* account for the majority of fALS cases, the causes of the sporadic ones, that represent 90–95% of ALS, are yet still largely uncertain and their genetics is still largely elusive [143]. Several studies suggest DNA damage in ALS, they are summarized in Table 3 and detailed in the next paragraphs.

4.2. Oxidative DNA damage to nucleic acids in Amyotrophic Lateral Sclerosis

In 1997 Ferrante and coworkers observed increased levels of 8-OHdG in the neuronal DNA extracted from the motor cortex

Table 3
Examples of DNA damage and related mutations observed in Amyotrophic Lateral Sclerosis.

Type of damage	Year/years	Main observations	References
Oxidative damage	1997	Evidence of oxidative DNA damage in ALS motor cortex and spinal cord	[144]
	2000–2008	Increased levels of oxidative DNA damage in plasma, urine, and CSF samples of ALS patients	[145,146,151]
Oxidative damage and DNA strand breaks	2001–2007	Evidence of mitochondrial damage, DNA strand breaks, and oxidative DNA damage in nuclear and mtDNA in early stage ALS animal models	[146–149]
	2014	Evidence that the ALS-associated protein FUS is required for the cellular response to oxidative DNA damage	[153]
Mitochondrial DNA (mtDNA) mutations	2000–2013	Evidence of mtDNA deletions in ALS brain, skeletal muscle and single motor-neurons	[164–167,169]
	2000–2013	Evidence of increased mtDNA point mutations in ALS tissues	[168,169]
Epigenetic-related damage	2013	Impaired dnmt3a levels and mtDNA methylation patterns in skeletal muscle and spinal cord of presymptomatic ALS mice	[171]
	2013–2014	ALS-associated FUS mutations impair the interaction between FUS and HDAC1 leading to increased DNA damage in ALS patients, and increased DNA damage, impaired transcription and splicing defects of critical genes in disease animal models	[172,173]

Abbreviations: ALS, Amyotrophic Lateral Sclerosis; CSF, cerebrospinal fluid; Dnmt3a, DNA methyltransferase 3a; FUS, fused in sarcoma; HDAC1, histone deacetylase 1.

of sALS patients, and in both sALS and fALS spinal cords [144]. Subsequently, increased levels of 8-OHdG were observed in plasma, urine, and CSF of ALS patients. Moreover, plasma and urine 8-OHdG levels increased significantly with time in the ALS group, and the rate of increase in urine was significantly correlated with disease severity [145]. A similar study aimed at evaluating oxidative damage in blood and CSF of either sALS or fALS patients showed that blood concentrations of hydroxyl radicals and CSF values of 8-OHdG and ascorbate free radical were higher in both groups of patients than in healthy matched controls [146]. Increased oxidative damage to the nuclear DNA, measured as the content of 8-OHdG, was also observed in the G93A-SOD1 transgenic mouse model of fALS [147], and oxidative mtDNA damage in spinal motor neurons of those mice occurs from the very early stages of the disease [148]. Others observed that in G93A-SOD1 mutant mice, motor neuron degeneration is characterized by somal and mitochondrial swelling and formation of DNA single-strand breaks prior to double-strand breaks occurring in nuclear and mtDNA. Single-strand breaks of nuclear DNA and mtDNA were evident in motor neurons of 6-week old mice, and double-strand breaks appeared by 9 weeks of age and progressively increased thereafter [149]. A selective decrease in the activity of the mtDNA-encoded enzyme cytochrome c oxidase (COX) was observed in spinal cord motor neurons of sALS patients, likely resulting from oxidative mtDNA damage leading to the accumulation of mtDNA mutations [150]. Murata et al. [151] measured the concentrations of the reduced and oxidized forms of coenzyme Q10 (CoQ10) and 8-OHdG levels in the CSF of sALS patients and age-matched healthy controls, observing increased levels of both oxidized CoQ10 and 8-OHdG in the CSF of sALS patients. Moreover, the percentage of oxidized CoQ10 was correlated with the concentrations of 8-OHdG, suggesting that both mitochondrial oxidative damage and oxidative DNA damage play important roles in the pathogenesis of sALS [151]. Significantly higher levels of oxidative DNA damage and DNA strand breaks, increased p53 activity, and a greater percentage of apoptotic cells were observed in SH-SY5Y neuroblastoma cells over-expressing the mutant G93A-SOD1 protein when compared to cells over-expressing wild-type SOD1 and untransfected cells [152]. More recently, it was shown that the ALS-associated protein FUS is recruited at sites of oxidative DNA damage by poly (ADP-ribose) polymerase (PARP-1) activity, suggesting that FUS is a component of the cellular response to DNA damage, and that defects in this response may contribute to ALS [153]. Similarly, mutant TDP-43 induced mitochondrial dysfunction and oxidative damage in motor neuron-like cells [154]. Collectively, those data suggest increased nuclear and mitochondrial DNA damage in ALS, likely contributing to mitochondrial dysfunction and death of motor neurons. Indeed, several investigators suggested that the accumulation of oxidative DNA damage in ALS motor neurons could result from impaired DNA repair capabilities in those cells [155]. We recently reviewed those studies that overall revealed that DNA repair mechanisms are activated following oxidative DNA damage in ALS tissues, and that impairments in DNA repair activities might contribute to the accumulation of DNA damage critical for motor neuron survival [155]. Particularly, a widespread PARP-1 activation, and an increased expression of BER enzymes were observed in ALS motor-neurons suggesting that DNA repair mechanisms could be activated following oxidative DNA attack in early stages of the neurodegenerative process. However, several investigators reported reduced/impaired BER activity in ALS-affected tissues, suggesting that following a persistent condition of oxidative stress in motor-neurons, DNA repair proteins, activated to counteract the oxidative insult, could be themselves the subject of ROS attack resulting in protein modification and degradation [155]. Studies attempting to evaluate the association between variants and polymorphisms of BER genes and sALS risk have been so far conflicting and inconclusive [156–163], suggesting that other mechanisms than mutation could be responsible for the impaired DNA repair activity observed in ALS tissues [155].

4.3. Mitochondrial DNA mutations in Amyotrophic Lateral Sclerosis

MtDNA is believed to be particularly sensitive to oxidative damage due to its proximity to the inner mitochondrial membrane, where oxidants are formed, and damage to the mtDNA by ROS can lead to mtDNA deletions, point mutations, and/or over proliferation, so that several studies have been performed in brain and muscle specimens of ALS patients aimed at evaluating the potential role of mtDNA mutations in the neurodegenerative process [164–169]. Dhaliwal and Grewal measured the levels of the common mtDNA deletion (mtDNA 4977-bp deletion) in brain tissues obtained from sALS patients and matched controls, observing that they were higher in the motor cortex in ALS than in controls [164]. MtDNA abnormalities, including respiratory chain defects, reduced levels of mtDNA, and mtDNA multiple deletions were also observed in skeletal muscles of sALS patients [165], and the analysis of the mtDNA 4977-bp deletion in muscle specimens from 36 sALS patients and 69 age-matched controls, revealed increased levels in the first group [166]. Following laser micro-dissection of single motor neurons from paraffin-embedded autopsy tissue, Mawrin and colleagues

analyzed the presence of the common mtDNA 4977-bp deletion. Spinal cord neurons showed slightly higher levels in ALS patients than in controls (94% vs. 75%), but no significant differences were found between patients and controls for neurons derived from other motor or non-motor regions [167]. In 2002, Wiedemann and coworkers also observed an increase of point mutations and a significant depletion of mtDNA in the spinal cord of ALS patients [168]. A recent study investigated mitochondrial genome structural alterations, including DNA lesions, point alterations and gross rearrangements, in three patients presenting with motor neuron disease. A higher frequency of mtDNA lesions, including multiple deletions, was observed particularly in the only *SOD1* mutated patient as well as in a patient negative for mutations in *SOD1* but presenting a severe form of the disease [169]. However, a recent analysis of European case-control studies suggests that common inherited variation in mtDNA (mtDNA haplogroups) is not involved in ALS susceptibility [170].

4.4. Other kinds of DNA damage in Amyotrophic Lateral Sclerosis

At best of our knowledge, little is known concerning other kinds of DNA damage or cytogenetic damage in ALS patients. Recent evidence however suggests that epigenetic mechanisms could contribute to DNA damage in ALS, and this will be discussed in the next paragraph.

4.5. Epigenetics and DNA damage in Amyotrophic Lateral Sclerosis

Mitochondrial Dnmt3a and DNA 5-methylcytosine (5-mC) levels have been investigated in human SOD1 transgenic ALS mice. Mitochondrial Dnmt3a protein levels were reduced significantly in skeletal muscle and spinal cord at pre-symptomatic or early disease stages, while 5-mC immunoreactivity was present in mitochondria of neurons and skeletal myofibers, and became aggregated in motor neurons of ALS mice. DNA pyrosequencing revealed significant abnormalities in 16S rRNA gene methylation in ALS mice. Immunofluorescence showed that 5-mC immunoreactivity can be sequestered into autophagosomes and that mitophagy was increased and mitochondrial content was decreased in skeletal muscle in ALS mice. The study revealed a tissue-preferential mitochondrial localization of Dnmt3a and presence of cytosine methylation in mtDNA of nervous tissue and skeletal muscle, demonstrated that mtDNA methylation patterns and mitochondrial Dnmt3a levels are abnormal in skeletal muscle and spinal cord of presymptomatic ALS mice, and revealed that these abnormalities occur in parallel with loss of myofiber mitochondria, overall indicating that not only oxidative DNA damage and mtDNA mutations, but also mtDNA epimutations, might represent early events in ALS pathogenesis [171].

A proper repair of damaged DNA requires that the damaged sequence is accessible to DNA repair proteins. Following the observations that the FUS protein is a component of the cellular response to DNA damage recruited at sites of oxidative DNA damage by PARP-1 activity [153], recent studies have demonstrated that fALS-associated *FUS* mutations impair the normal interaction between FUS protein and histone deacetylase 1 (HDAC1) resulting in deficient DNA repair [172,173]. Particularly, increased DNA damage was observed in motor cortex samples from human ALS patients harbouring *FUS* mutations [172], and increased oxidation, transcription and splicing defects were observed in genes that regulate dendritic growth and synaptic functions in mice harbouring fALS-associated FUS mutation [173]. Indeed, there is increasing evidence indicating that epigenetic HDAC proteins such as sirtuin 1 (SIRT1) and HDAC1 play a role in the DNA damage response of postmitotic neurons, and that neurons lacking either SIRT1 or HDAC1 are more susceptible to DNA damaging agents and are deficient in double strand break repair [174]. Taken overall, those studies reinforce the hypothesis of interplay between DNA damage, epigenetic pathways and repair pathways that, if impaired, could contribute to neurodegeneration.

5. Conclusions

In the present manuscript we reviewed the most significant studies performed in post-mortem neuronal material and in peripheral tissues of patients affected by one of the three major neurodegenerative diseases, namely AD, PD, and ALS, and aimed at evaluating the extent of DNA and chromosome damage in those conditions. Several similar results have been obtained in animal and cell culture models of those diseases or in other neurodegenerative diseases [110], that have not been discussed, unless of extreme relevance, due to space allowance. There is agreement that oxidative DNA damage, mainly to the mtDNA, is one of the earliest detectable events in early stages of the neurodegenerative process, and may contribute to mitochondrial dysfunctions thereby perpetuating the oxidative stress in neurons, ultimately leading to neurodegeneration [2,8,25–29,37,108,146–149]. As suggested by many authors, oxidative DNA damage might result from an age-related decline in antioxidant defences and DNA repair functions [110], might be induced by environmental exposure to neurotoxicants [6], or could also represent a consequence of the neurodegenerative process itself [7,110]. Very arguing are the novel hypotheses, developed in recent years, suggesting that early life exposures can induce epigenetic changes leading to long-lasting effects and increased DNA damage later in life [14,82–84,94]. Within this context there is emerging evidence linking proteins involved in signalling and repair of DNA damage to epigenetic proteins such as HDACs [172–174], and there is indication that perturbations of the DNA methylation potential could contribute to epigenetic-mediated changes of DNA repair gene expression [94]. Furthermore, the hypothesis that epimutations of the mtDNA could contribute to mitochondrial dysfunction and neurodegeneration, alongside with mtDNA damage and mutations, is arguing and warrants further investigations [171]. For what concerns AD, there seems to be a preferential occurrence of chromosome malsegregation events in affected brain neurons and peripheral cells [63–68,77], and increasing evidence points to a contribution of impaired folate metabolism and related epigenetic mechanisms at the basis of such a tendency [85–90,96]. Overall, there is no doubt that DNA damage contributes to the onset and the progression of neurodegeneration, and research is warranted to completely understand the links between epigenetic processes, DNA damage and repair in neurodegenerative diseases.

Conflict of interest statement

The authors declare no conflicts of interest.

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