DNA Repair 12 (2013) 568–577

Contents lists available at SciVerse ScienceDirect

DNA Repair

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

Nucleotide excision repair in chronic neurodegenerative diseases

Sara Sepe[a], Cesar Payan-Gomez[a,c], Chiara Milanese[a,b], Jan H. Hoeijmakers[a], Pier G. Mastroberardino[a,*]

[a] Department of Genetics, Erasmus Medical Center, Rotterdam, The Netherlands
[b] RiMED Foundation, Palermo, Italy
[c] Facultad de Ciencias Naturales y Matemáticas, Universidad del Rosario, Bogotá, Colombia

ARTICLE INFO

Article history:
Available online 28 May 2013

Keywords:
Neurodegeneration
DNA damage
Parkinson's disease
Alzheimer's disease
Huntington's disease
Transcriptomics

ABSTRACT

Impaired DNA repair involving the nucleotide excision repair (NER)/transcription-coupled repair (TCR) pathway cause human pathologies associated with severe neurological symptoms. These clinical observations suggest that defective NER/TCR might also play a critical role in chronic neurodegenerative disorders (ND), such as Alzheimer's and Parkinson's disease. Involvement of NER/TCR in these disorders is also substantiated by the evidence that aging constitutes the principal risk factor for chronic ND and that this DNA repair mechanism is very relevant for the aging process itself. Our understanding of the exact role of NER/TCR in chronic ND, however, is extremely rudimentary; while there is no doubt that defective NER/TCR can lead to neuronal death, evidence for its participation in the etiopathogenesis of ND is inconclusive thus far. Here we summarize the experimental observations supporting a role for NER/TCR in chronic ND and suggest questions and lines of investigation that might help in addressing this important issue. We also present a preliminary yet unprecedented meta-analysis on human brain microarray data to understand the expression levels of the various NER factors in the anatomical areas relevant for chronic ND pathogenesis. In summary, this review intends to highlight elements supporting a role of NER/TCR in these devastating disorders and to propose potential strategies of investigation.

1. Introduction

Defects in genome maintenance, and in nucleotide excision repair (NER) pathway in particular, cause human pathologies associated either with high cancer predisposition and/or severe neurodevelopmental abnormalities. Rare inherited NER syndromes fall into two classes: xeroderma pigmentosum (XP) is dominated by a strong, sunlight-induced skin cancer predisposition and, in some patients, by accelerated neurodegeneration. Cockayne syndrome (CS), and related conditions such as trichothiodystrophy are characterized by severe neurodevelopmental abnormalities. Patients with the XP/CS complex have mixed symptoms and present with skin and eye disease of XP and the somatic and neurological abnormalities of CS [1]. These clinical observations lend support to the concept that defective NER might also play a critical role in chronic neurodegenerative disorders (ND), such as Alzheimer's and Parkinson's disease. This hypothesis is further substantiated by the evidence that aging is the principal risk factor for these diseases, and that NER is very relevant for the aging process itself [2]. A role of NER in the pathogenesis of AD and PD is also consistent with the notion that environmental factors are also critical in the onset of these neurodegenerative diseases, as NER deals with stochastic DNA damage, which is at least in part of environmental origin. In addition, because neurons are postmitotic cells and regeneration in the brain is very limited, it is perfectly conceivable that these cells require particular care for maintenance of genetic fidelity, and chronic defects in the machineries in charge might result in pathology.

Our understanding of the exact role of NER in chronic ND, however, is extremely rudimentary; while there is no doubt that defective NER can lead to neuronal death, evidence for its participation in the etiopathogenesis of ND is inconclusive thus far. Identification of pathogenic mechanisms and potential therapeutic targets is a topic of extreme relevance, especially in consideration of the anticipated social burden of ND in the fast-aging population of industrialized countries. Further focused investigations are therefore very pertinent and certainly required to unambiguously demonstrate a role of NER in these pathologies. In this review, we would like to summarize the experimental observations supporting a role for NER in chronic ND and to suggest questions and lines of investigation that might help in addressing this important issue.

2. Nucleotide excision repair

NER is divided into two pathways, GG-NER and TC-NER, which differ in the first step. The first branch is responsible for repair of

* Corresponding author.
E-mail address: p.g.mastroberardino@erasmusmc.nl (P.G. Mastroberardino).

1568-7864/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.dnarep.2013.04.009

the wide class of general helix-distorting lesions anywhere in the genome, while the second repairs lesions blocking the RNA polymerase activity and therefore elongation during transcription [3,4]. The spectrum of lesions eliminated by both systems is at least in part non-overlapping. TC-repair most likely involves additional and poorly characterized factors that might remove also transcription-blocking lesions caused by oxidation of the bases, which are not the substrate of GG-NER [5,6].

In GG-NER the protein XPC is believed to be the first main factor to bind damaged DNA [7]. XPC recognizes bulky distortions in the helix structure caused by the lesion and might act in concert with other accessory partners having diverse functions, which in some cases are still poorly understood. HR23, a homologue of Rad23 – which exists in two isoforms, HR23A and HR23B – is probably involved in XPC polyubiquitination, which might increase its affinity for DNA. CEN2 is an optional factor that may stabilize the complex [8,9]. The DDB complex, formed by XPE and DDB2, enhances DNA distortion to facilitate recognition by XPC [8]. Once the damage is recognized, XPC binds the repair/transcription factor TFIIH and facilitates its interaction with the lesioned DNA. The TFIIH factor consists of ten subunits, seven of which compose the core of the complex (XPD, XPB, p62, p52, p44, p34 and TTDA). Other three subunits (CDK7, MAT1, and Cyclin H) form the so-called *cyclin activating kinase-subcomplex*, which is connected to TFIIH core via interaction with XPD [10]. The TFIIH multimeric complex is stabilized by the XPG factor [11]. XPB and XPD are 5′-3′- and 3′-5′-DNA helicases respectively, which unwind the helix in proximity of the lesion [12]. This unwinding process separates the two DNA filaments and generates two short single strand stretches, which facilitate the recruitment of a further complex, composed by XPA, which has affinity for chemically altered DNA, and the ssDNA binding protein RPA1 which binds the non-damaged strand). The fundamental function of this pre-incision complex is to stabilize the open DNA structure [13,14].

The next step involves endonucleolytic cleavage and excision of the damaged and now uncoiled ssDNA. The process is performed by two endonucleases, the dimeric XPF-Ercc1 complex, which cuts at the 5′ end of the ssDNA, and the XPG factor, which cuts at the 3′ end [15]. This process results in a single stranded gap in the genome and a single stranded oligonucleotide fragment that is excised. The latter typically comprises 27–30 nucleotides.

The gap is filled by de novo synthesis of DNA by DNA-polymerase complexes that include polymerase δ, κ, and ε. These enzymes are recruited by the PCNA clamp in association with factors that are specific for the polymerase type. Polδ is recruited by RPA, the clamp loader RCF, and p66, while polε requires the CTF18-RCF clamp loader. Polκ is instead recruited by ubiquitinated PCNA and XRCC1 [16].

The final step is DNA ligation, which can be performed by two different enzymes. DNA ligase 1 operates exclusively during the S phase of the cell cycle, while DNA ligase IIIa-XRCC1 complex operates throughout the whole cell cycle [17].

TC-NER repairs lesions that block RNA polymerase II and therefore interfere with the vital process of transcription. TC-NER differs from GG-NER in the first step, recognition of the damage, which is carried out in TC-NER by the elongating RNA polymerase. Here, three proteins, CSB, CSA, and XAB2 are involved in poorly defined steps of making the lesion accessible to NER factors presumably by backtracking of the RNA polymerase and recruitment of XPG and TFIIH after which the remainder of the NER reaction may proceed as for GG-NER [18]. Indirect evidence supports the idea that transcription-blocking different than NER repaired ones are made accessible by CSB, CSA, XPG, and TFIIH to a different DNA repair process called base excision repair (BER). The latter deals with more subtle DNA damages that include many oxidative lesions. The total of TC-NER and presumed TC-BER is designated here as transcription-coupled repair (TCR).

Since GG-NER operates genome wide, defects in this subpathway result in broadly diffused accumulation of damage (except for the transcribed strand of active genes where TCR still takes care for lesion removal). As a consequence of global genome lesion accumulation, GG-NER defects lead to enhanced mutations and hence cancer; In fact, GG-NER defects are associated with the cancer syndrome XP. On the other hand, defects in TCR cause damage that interferes with transcription and favors cell death. Interestingly, impairment of TCR is strongly associated with the neurodevelopment abnormalities in CS, XP/CS and other CS-like syndromes and in the corresponding mouse models [19].

3. Neurodegeneration

Neurodegenerative diseases (ND) are characterized by a slow, chronic, and progressive neuronal loss. The latter, at least in initial stages of the pathogenesis, is confined to distinctive areas and affects only specific neurochemical types of neurons [20–23]. This regional specificity underlies the diverse symptomatology of the various ND, because different brain functional and anatomical domains command different abilities. These crucial features should not be neglected in investigations aimed to identify novel pathogenic mechanisms because neuronal death is an endpoint that might be caused by multiple and converging detrimental cascades. Not every deleterious mechanism belongs to the etiopathogenesis of ND and, while derangement in certain processes (e.g. NER/TCR) might lead to neuronal loss, this does not necessarily imply that the process itself is intrinsic to the ND pathobiology. Involvement in ND pathogenic cascades should be therefore inferred upon unambiguous evidence that perturbation of the considered mechanism reproduces pathological hallmarks of chronic ND and leads to physiological alterations recapitulating human diseases. Assays to address mechanisms' participation in pathogenesis should be performed in reference to a panel of appropriate and reliable indicators that confirm affinities with human ND. The choice of such markers, however, has been a source of contention for long time. An intrinsic problem is that, despite sharp differences in clinical manifestations, different ND also share several functional defects. Mitochondrial dysfunction, altered protein homeostasis, redox imbalance, and calcium dysregulation are only some examples of anomalies observed in all major chronic ND [24–26]. These processes, however, are rather vulnerable per se; accordingly, their alteration is observed in many conditions that have little, or nothing to do with chronic ND [27,28] and thus they rather reflect a general state of ongoing pathology. Accordingly, they are also associated with broader signs of distress, which interest neuronal and non-neuronal cells and include dystrophic neurites and activation of astrocytes and microglia [29]. This concept obviously applies to NER as well and, while defective DNA repair might certainly elicit neurological alterations, the question whether this is enough to state unambiguously that it is relevant for chronic ND remains open.

In this respect, assessing regional specificity of cellular dysfunctions might unambiguously point out the relevance of a mechanism for ND pathogenesis. In fact, at least in initial stages, cell death is confined to distinctive areas and interests only specific neurochemical types of neurons. For instance, in Parkinson's disease, only neurons using dopamine degenerate, and only in the *substantia nigra pars compacta*. This feature underlies the diverse symptomatology of the different neurodegenerative diseases, because brain anatomical domains govern different functions. It is important to highlight that neuropathology and its anatomical pattern are highly dynamic and evolves and spreads in the course of the diseases

[21]. The reconstruction of the spatiotemporal progression of ND has been mostly determined by evaluating the presence of protein aggregates as well as cell death in human autopsies. At present, the presence of aggregates still remains the gold standard to assess pathology and this should be considered when evaluating candidate processes suspect of contributing to ND. The diagnostic value of aggregates to determine ongoing neuropathology is unquestioned. Their precise function in the pathogenic cascade, however, is still debated. For instance, the studies to define the pathologies' staging are based on immunochemical approaches that detect relatively large form of aggregates, while structural and functional studies suggest that the most toxic forms are rather small, soluble oligomers [30].

To facilitate the reader, we would like to summarize the anatomopathological features of two common chronic ND, Alzheimer's (AD) and Parkinson's disease (PD), as well as of a rare condition, Huntington's disease (HD). We opted for this approach because most cases of AD and PD are sporadic forms, in which etiology cannot be ascribed to mutations in single genes and should be rather sought in complex interactions between genes and environment [31]. Conversely, HD is a monogenetic autosomal dominant disorder, in which pathology is caused by a specific polyglutamine expansion in the huntingtin (HTT) gene. Despite the very diverse etiology, the three disorders present significant overlapping in pathology [32–34], demonstrating once again that several functional anomalies can be common between diverse ND.

Alzheimer's disease (AD) is the most frequently encountered form of dementia and symptoms include memory impairment and severe cognitive loss. The fundamental hallmarks in AD neuropathology are extracellular amyloid plaques and intracellular neurofibrillary tangles (NFT). Amyloid plaques are spherical deposits of fragments 40–42 aminacid fragments of the amyloid-beta (Abeta) protein [35]. NFT are composed of paired helical filaments (PHFs) of the microtubule-associated protein tau and thus consist fundamentally of disorganized microtubules. These two elements interact; Abeta-40 and -42 form stable complexes with soluble tau [36] and there is a synergistic effect of amyloid aggregation in the propagation of tau pathology [37].

In AD, pathology mostly affects the cerebral cortex. The latter is divided into neocortex and allocortex. The neocortex constitutes the outer layer of the cerebral hemispheres and is the anatomical structure that in generically referred to as cortex. The allocortex is, in terms of evolution, the oldest part of the cortex, is rather buried in the medial ventral part of the brain and includes several formations, among which the hippocampus. The allocortex is particularly affected in AD and neuropathology begins from its entorhinal and transenthorinal regions of the allocortex, to progress in the hippocampus Ammon's horn and to spread in the final stages to the neocortex [20,38–40]. Dysfunctions in these anatomical areas, which participate to memory as well as behavioral aspects of the personality, are reflected in the symptoms of AD.

Parkinson's disease (PD) is a common motor disorder. The majority of PD cases are idiopathic (around 90%); as for familial forms, sixteen loci responsible for familial forms have been identified thus far. These include both autosomal dominant (alpha-synuclein and LRRK2) and autosomal recessive genes (e.g. parkin, DJ-1, and PINK1) [41]. The most prevalent PD-associated gene is LRRK2. PD clinical presentation concerns basic movements and includes tremors, bradykinesia, rigidity, and postural instability. The spectrum of symptoms, however, is not confined to motor signs, and includes other manifestations such as neuropsychiatric disturbances [42]. Overall, PD results in severe debilitation, reduced quality of life, and early institutionalization.

PD is a disease of the basal ganglia, pathology mostly affects the nigro-striatal dopaminergic (DA) circuits and in particular neurons in the *substantia nigra pars compacta* (SNC), which are responsible for the fine-tuning of motor capacities [43]. DA neurons of the adjacent VTA, which are instead involved in mood functions including reward and motivation and differ in their physiology [44], are spared. One of the principal hallmarks of PD neuropathology is the presence of aggregates primarily containing the protein alpha-synuclein, also known as Lewy's bodies. Just as in AD, the pathoanatomy of PD has been characterized assessing the presence of aggregates, formed in this particular case by alpha-synuclein [45]. Despite the midbrain is the most affected area, there is evidence that the pathology initiates in the motor nuclei of the medulla oblongata, proceeds through the pontine nuclei – the locus ceruleus and the Raphe nucleus in particular – and only subsequently expands to the midbrain. At more advanced stages the pathology spreads also to the neocortex [21,45].

Huntington's disease is a dominant, monogenic neurodegenerative disorder [46]. Clinical manifestations include progressive loss of gross motor skills and the development of chorea – which consists of abrupt, involuntary movements. Motor defects are not limited to impairment of gross abilities and also fine motor skills deteriorate earlier in the course of HD. Other important neurological signs include neuropsychiatric symptoms and cognitive impairment. Effective therapies for this devastating disease are not currently available and, after a typical latency of 20 years from diagnosis, HD invariably culminates in premature death [47].

HD is caused by a mutation in the coding part of the huntingtin gene that results in abnormally expanded CAG trinucleotide repeats. Consequently, the translated protein huntingtin protein contains disease-causing expansions of glutamines (polyQ) that make it prone to misfold and aggregate and immunostaining of HD brains revealed htt- and ubiquitin-positive intranuclear inclusions [48,49]. In Huntington's disease the basal ganglia, are mostly affected, in particular the caudate nucleus and the putamen of the striatum. The pathology is selective for certain neuronal populations, such as medium-sized projection spiny neurons (MSNs), while others, such as aspiny interneurons are relatively spared [22,50]. MSNs use the neurotransmitter gamma-aminobutyric acid (GABA) and exert an inhibitory effect in the basal ganglia circuits; the uncontrolled choreic movements typical of HD have been ascribed to the loss of this inhibitory input [51].

4. NER and neurodegeneration

The functional alterations involved in ND have been extensively studied in relation to some forms of DNA damage, and to BER in particular. Here, the rationale stems from the observation that a prominent outcome of these dysfunctions is oxidative stress, with consequent oxidative modifications to DNA that are mostly, but not exclusively repaired by BER. This subject has been excellently reviewed [52]. Other DNA repair mechanisms, however, might have great relevance for neurodegenerative diseases, also in consideration of the lack of unambiguous evidence that the BER system might act in concert with transcription [53,54].

As anticipated, NER/TCR is important for proper function of the nervous system, as highlighted by neurological phenotypes associated with NER/TCR disorders in humans [53,55]. Our depiction of the role of NER/TCR in neurodegeneration, however, is still blurred and highly rudimentary, and very few studies can be found in the available literature. The complexity of the NER pathway, which involves several players, complicates the scenario and, within the same pathology, mutations in different genes result in diverse neurological problems [56]. Additional complexity is generated by the possibility that defects in the CNS are a consequence of alterations in peripheral organs (e.g. kidney or liver), which lead to metabolic anomalies with repercussions on the brain. For instances, in *Ercc1* knock-out mice one the principal causes of illness, if not the

principal one, are liver defects, which affect the organism systemically [57]. In this model, the strength of the genetic defect is such that deterioration proceeds too fast and does not allow careful neuropathological analysis. When the *Ercc1* defect in liver is rescued – with the other tissues still carrying the mutated alleles – neurological defects can be detected, especially at the level of the cerebellum. The anomalies, however, seem rather associated with kidney failure and consequent increased proteinuria and thus the pathology falls into the category of uremic encephalopaties. In the same study, target deletion of *Ercc1* in the brain through Cre-lox technology – using an *Ercc1* floxed allele in combination with a nestin promoter driven Cre recombinase – results in lower grow rates and premature death. These signs indeed support a critical role of *Ercc1* in the brain, even though the authors state that at the time of publication no accurate neurological analysis had been performed, and therefore precise details could have not be inferred [57].

Two more recent studies provide additional evidence advocating the importance of Ercc1 in brain function. One study focused on the cortex and the hippocampus, and is therefore more relevant for AD pathogenesis, and demonstrates that *Ercc1* mutants expressing only a truncated allele with reduced activity [58] exhibit mild, but progressive neurodegeneration [59]. At 4 months of age, these models present neuropathological signs such as argyrophilic neuronal profiles indicating cell death as evidenced by silver staining, as well as caspase-3 and p53 activation. Neuropathology is associated with electrophysiological impairment and in particular with reduction of hippocampal synaptic plasticity. The latter is relevant for AD because impairment in synaptic plasticity is robustly observed in animal models [60] and reflects loss of memory in patients [61,62]. These finding were also recapitulated in mice in which *Ercc1* deletion was exclusively targeted to excitatory postnatal forebrain neurons using Cre-lox technology and driving recombinase expression under the CaMKII promoter [59].

These models also exhibit robust gliosis, a further sign of neuropathology associated also with chronic ND [63,64]. ND pathogenesis, in fact, causes alterations not only in neurons, but also in glial cells. Whether these perturbations are toxic or not it is still object of debate; microglial activation is seen usually as a detrimental event, at least at advanced stages. More recent evidence, however, suggests that also "good" microglia exist, probably playing a role at early stages of disease [65]. Astrocytes activation is considered protective becuase these cells provide support by several means, including production of trophic factors, calcium buffering, and supply of reducing equivalents [66]. The role of NER in these cells, however, is largely obscure. Components of the NER machinery have been detected in astrocytes [67], and it has been reported that cultured astrocytes have similar NER capacity than neurons [68]. To our best knowledge, no information is available on NER in microglia. This issue has not been investigated in models of chronic ND or in patients' brain autopsies thus far. It is therefore perfectly conceivable that NER dysfunction might play a role also in glial cells in ND, but no experimental data are currently available to support this hypothesis. Also in this case, additional studies are required.

Another study, which was also focused on the hippocampus, performed expression profile analysis in *Ercc1* knock-out mice at post-natal day 21, demonstrating a suppression of cholesterol synthesis in this brain region [69]. These findings certainly deserve further experimental attentions because alterations in cholesterol metabolism are known to occur in chronic ND. In AD, mutations in the gene ApoE, which codes for the principal cholesterol transporter in the brain, constitutes a primary genetic risk factor [70,71] and cholesterol itself facilitates Abeta aggregation [72]. Epidemiological studies confirm that individuals with high levels of blood cholesterol are at higher risk for AD [73]. Also in HD, alterations in cholesterol metabolism resulting in decreased levels occur during pathogenesis [74]. The cases of AD and *Ercc1* mutants differ in that the former is associated with increased cholesterol, while the latter with suppression of its biosynthesis. Nevertheless these elements clearly point to a role of cholesterol metabolism in neurodegeneration – possibly involving reactive genotoxic intermediates – and draw a potential link with genomic instability driven by *Ercc1* mutations. Additional investigations are necessary to unravel the details of these phenomena. Signs of neuropathology caused by *Ercc1* deficiency also develop in the motor neurons in the peripheral nervous system, lending further support to the importance of this enzyme in post-mitotic neuronal cells [75].

The above-mentioned studies clearly demonstrate the importance of *Ercc1* in maintenance of proper neuronal function. *Ercc1*, however, plays a role also in other DNA repair systems than GG-NER and TC-NER, for instance repair of the very toxic inter-strand cross links and double strand breaks; thus, the described data do not provide unambiguous information on the importance of NER in the brain. This issue also touches other members of the NER system; for instance, CSA and CSB operate in TC-NER, but it is also likely that they participate to the broader TCR pathway, which includes transcription-blocking non-NER lesions. Two factors, however, are rather NER specific: XPA is involved in GG-NER and TC-NER, and XPC is implicated exclusively in GG-NER. The clinical symptoms of XPC patients and corresponding mice are dominated by cancer predisposition, linking defects in GG-NER with carcinogenesis, but no appreciable neurodegeneration is noted [76,77]. XPA patients and KO mice also exhibit a cancer phenotype [78]. While XPA knockout mice do not suffer from neuronal loss, XPA patients display additional signs of accelerated neurodegeneration starting in the second decade of life. [55]. These findings suggest some important considerations. Firstly, a clear-cut defect in NER or TC-NER is not sufficient to elicit overt brain pathology in mice and synergistic combinations with defects in other DNA repair systems are required. Indeed, robust signs of neurodegeneration are observed in double mutants in which ablation of XPA or XPC has been combined with genetic deletion of other DNA repair factors, such as CSB or CSA [55]. The combined presence of these mutations results in drastic disruption of the DNA repair pathways, which rapidly induce strong phenotypes [55]. In fact, observation of neurological phenotypes is possible only under limitation of systemic deterioration and therefore investigations must be performed in models in which the double mutation is restricted to determined anatomical areas of the brain. As previously mentioned, this is usually achieved taking advantage of the Cre-lox technology. Here an example comes from Jaarsma and colleagues, who investigated the effects of the combination of targeted disruption of *Xpa* in the excitatory forebrain neurons on a *Csb*−/− background [55].

Again, these models with multiple mutations provide direct evidence that DNA maintenance is fundamental for neuronal survival. However, deterioration remains aggressive, and the question whether the underlying mechanisms responsible for cell death are comparable with those observed in chronic and slow progressing ND is still open. This controversy permeates from the state-of-the-art of research, which thus far demonstrated that DNA repair deficiency is associated with terminal cellular and molecular phenotypes that indicate neuronal death (e.g. argyrophilia in silver staining or caspase activation), without providing insights on specific upstream mechanisms. Future studies should therefore approach NER/TCR models with systematic investigation focused on characteristic pathways intrinsic to the pathogenesis of chronic ND. Amenable approaches include assessment of defects in the activity of mitochondrial respiratory complexes (e.g. complex I deficiency in PD), formation of insoluble and/or ubiquitinated aggregates in specific neuroanatomical areas, neurochemical profiling of neurotransmitters, or alterations in redox homeostasis in selected neuronal types. Anomalies in these mechanisms constitute

specific hallmarks and, for instance, impairment in Complex I or Complex II driven respiration are typical of PD and HD respectively [79–81], while decreased Complex IV activity has been reported in AD [82,83]. Additional examples are altered dopamine metabolism and oxidation of dopaminergic neurons in the *substantia nigra* during PD pathogenesis [84,85] or, as previously discussed, formation of insoluble aggregates in specific areas, which occurs distinctively in AD, PD, or HD [86].

It is essential to emphasize that these approaches might provide crucial insights also when applied to DNA repair deficient models without overt neurodegeneration (e.g. *Xpc* or *Xpa* knock-outs). In fact, there are several examples in this field in which genetic mouse models of ND do not exhibit an overt phenotype; nevertheless, these animals have been proven very useful to gather information on the pathogenesis. A paradigmatic example here comes from models of autosomal recessive genetic PD. Modeling mutations in Parkin, DJ-1, or PINK1 in rodents led to a negligible phenotype, with no signs of progressive degeneration in the dopaminergic neurons of the *substantia nigra* [87]. A comparable case is that of the AD mouse model Tg2576sw, which overexpresses the 695-amino acid isoform of human Abeta precursor protein containing the K670N and M671L double mutation (known as Swedish mutation) [88]. Tg2576sw mice do not present neuronal loss in the CA1 region or loss of synaptic density in the hippocampus dentate gyrus, even at advanced ages [88]. Similarly, genetic knock-in models of HD expressing the expanded polyQ stretch in the endogenous htt protein fail to develop any overt symptoms, even though closer examinations revealed subtle changes in mice with longer repeats [89–91]. Despite the negligible or even absent neuronal loss, these models provided invaluable information on the pathogenic mechanisms. For instance, studies on the AD Tg2576sw model demonstrated that loss in synaptic integrity precedes electrophysiological defects (i.e. long term potentiation deficits) and occurs far before deposition of amyloid plaques [60]. In a comparable manner, transcription profiling on a double mutant of PD expressing alpha-synuclein carrying both the A53T and A30P variants, which exhibit modest neuropathology [92], revealed gene-dose dependent dysregulation of several transcripts relevant for dopaminergic neurons. Importantly, these alterations precede neuropathology and emphasize the concept that subtle molecular changes anticipate cell loss and functional deficits [93]. Future in-depth investigations exploring molecular pathology in NER models with no overt degeneration might improve our understanding of the role of this pathway in chronic neurodegeneration and determine the extent of overlap between NER/TCR deficiency in the brain and neurological disorders.

5. Anatomical pattern of expression of NER factors in the human brain

A potential hypothesis explaining regional specificity characterizing ND could envision that expression of genes involved in the pathogenesis differs among brain areas following an anatomical pattern reflecting that observed in ND. Thus, expression of genes with protective functions, for instances NER/TCR factors, might be significantly lower in those areas subject to deterioration. At present, and to our best knowledge, no reports address this important issue. To gather initial and preliminary insights, we performed meta-analysis on datasets from five microarray experiments on human brains available from the open source repository of the Allen Institute for Brain Science (Allen Human Brain Atlas, http://human.brain-map.org/) [94]. We focused on 38 genes with proven involvement in NER and on anatomical regions affected in AD, PD, and HD (see Tables 1 and 2). We also included different areas of the cerebellum, which is not involved in the discussed pathologies, as an external control.

Table 1
List of the genes involved in NER/TCR considered in this review.

Brain area	Symbol
Ammons Horn – CA1 field	CA1
Ammons Horn – CA2 field	CA2
Ammons Horn – CA3 field	CA3
Ammons Horn – CA4 field	CA4
Cerebellar Cortex Crus I Lateral Hemisphere	CbCx Crus I Lateral Hemisphere
Cerebellar Cortex Crus I Paravermis	CbCx Crus I Paravermis
Cerebellar Cortex Crus II Lateral Hemisphere	CbCx Crus II Lateral Hemisphere
Cerebellar Cortex Crus II Paravermis	CbCx Crus II Paravermis
Cerebellar Cortex I-II	CbCx I-II
Cerebellar Cortex III Paravermis	CbCx III Paravermis
Cerebellar Cortex III	CbCx III
Cerebellar Cortex IV	CbCx IV
Cerebellar Cortex IV Paravermis	CbCx IV Paravermis
Cerebellar Cortex V	CbCx V
Cerebellar Cortex V Paravermis	CbCx V Paravermis
Cerebellar Cortex VI	CbCx VI
Cerebellar Cortex VI Lateral Hemisphere	CbCx VI Lateral Hemisphere
Cerebellar Cortex VI Paravermis	CbCx VI Paravermis
Cerebellar Cortex VIIAf	CbCx VIIAf
Cerebellar Cortex VIIAt	CbCx VIIAt
Cerebellar Cortex VIIB	CbCx VIIB
Cerebellar Cortex VIIB Lateral Hemisphere	CbCx VIIB Lateral Hemisphere
Cerebellar Cortex VIIB Paravermis	CbCx VIIB Paravermis
Cerebellar Cortex VIIIA	CbCx VIIIA
Cerebellar Cortex VIIIA Lateral Hemisphere	CbCx VIIIA Lateral Hemisphere
Cerebellar Cortex VIIIA Paravermis	CbCx VIIIA Paravermis
Cerebellar Cortex VIIIB	CbCx VIIIB
Cerebellar Cortex IX	CbCx IX
Cerebellar Cortex IX Paravermis	CbCx IX Paravermis
Dentate Gyrus	DG
Locus Ceruleus	LC
Raphe Nuclei	Raphe Nuclei
Olfactory Parolfactory Gyri	PaG
Olfactory Subcollosal Gyrus	SGC
Globus Pallidus External Segment	GPe
Globus Pallidus Internal Segment	GPi
Red Nucleus	R
Head of Caudate Nucleus	HCd
Nucleus Accumbens	Ac
Putamen	Pu
Tail of Caudate Nucleus	TCd
Substantia Nigra Compact Part	SNC
Substantia Nigra Reticular Part	SNR
Ventra Tegmental Area	VTA

In general, NER factors are indeed expressed in human areas related to ND and an initial screen reveals that about 30% of the 38 canonical genes involved in NER/TCR are detectable in most regions (Fig. 1). It is interesting to note that – at least in physiological conditions and in the absence of pathogenesis – the number of NER/TCR factors expressed in areas degenerating in AD and PD is generally lower than the cerebellum, which is not significantly affected in these diseases. To derive additional and more rigorous insights about the influence of the NER/TCR system in the different anatomical regions, we performed two-way cluster analysis. Areas with similar pattern of expression of NER genes were grouped together using Euclidean distance. We considered areas involved in the pathogenesis of AD, PD, or HD, as detailed in Table 1. This approach provided several clues. At a first glance NER factors profiles can be divided in two categories, the first of which has highly ubiquitous expression in all the studied regions (Fig. 2, right portion), and a second group of comparable size that is expressed at different levels in different areas, and thus has more specific pattern (Fig. 2, left portion). The genes responsible for the initial recognition step of the GG-NER are distributed between the two clusters, with XPC and DDB2/XPE in the low and DDB1, CETN2, HR23A, HR23B in the high expression group. This observation is

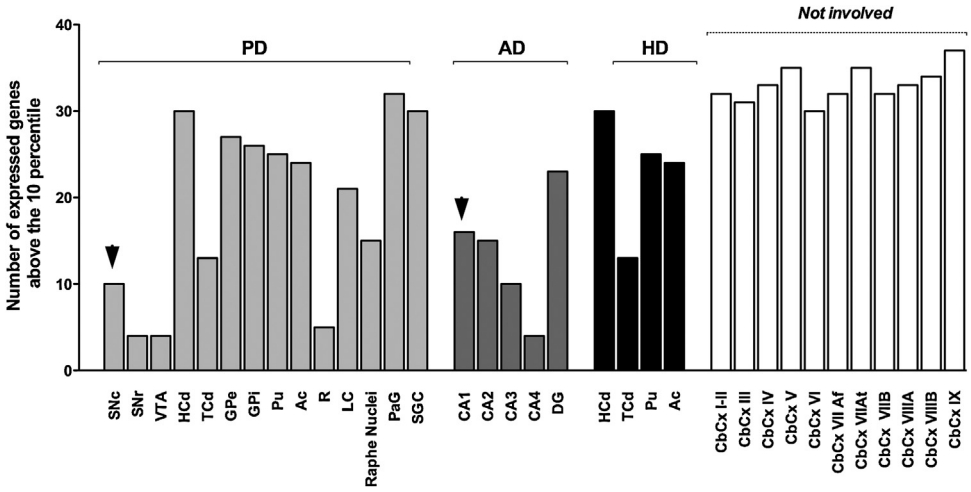

Fig. 1. We considered several brain areas related to, but not necessarily degenerating in ND and determined how many of the NER/TCR factors are expressed above the 10-percentile threshold. In PD, at early stages degeneration in mostly observed in dopaminergic neurons of the SNpc (arrow). The other areas are included because there are in anatomical proximity (e.g. SNr), because contain neurons that do not degenerate despite same neurochemical properties (e.g. VTA), because they belong to the same neuronal circuits (HCd, TCd, GPe, GPi, Pu, and Ac), because they degenerate at later stages (LC, Raphe Nuclei), or because present anomalies in PD patients (R, [103,104]). In addition, we included the olfactory bulb (PaG and SGC) because olfaction is a common prodromal symptom in PD [105] (reviewed in [106]). In AD, degeneration begins in the CA1 region of the hippocampal formation (arrow) and expands to the other areas only to later stages. In HD the striatum, which includes HCd, TCd, Pu, and Ac, is the most affected region; however only a subset of neurons in these areas die.

intriguing because it challenges current thinking suggesting that GG-NER is not essential in post-mitotic neurons [54]. Moreover, the Xpc protein appears to be one of the rate-limiting factors in GG-NER [95], whereas also DDB2/XPE is the essential subunit specific for detection of a subset of lesions in GG-NER.). A significant role of GG-NER in protecting from accelerated neurodegeneration is supported by recent findings indicating that *Xpc*−/− mice display a mild yet significant neurological phenotype [55].

Interestingly, genes in the recognition step of the TC-NER fall all in the low expression group. Obviously, low expression levels do not necessarily imply irrelevance for proper cellular function and other influencing factors, for instances sharp changes in expression, might occur under distressful conditions. Therefore low levels of transcription in genes responsible for the initial steps of TC-NER does not exclude that this process is important for neurons. In fact, Cockayne syndrome patients with CSA of CSB mutations develop neurodegeneration, even though we still lack conclusive evidence that symptoms are due intrinsic effects of the mutations on neurons, and not systemic consequences of peripheral defect [57]. The latter issue has been challenging also in consideration of the absence of overt neurological phenotype in *Csa* or *Csb* knock-out mice [96,97]. A further consideration on the role of low expressed NER genes in neurodegeneration comes from DBB2, which was identified as novel risk locus in Progressive

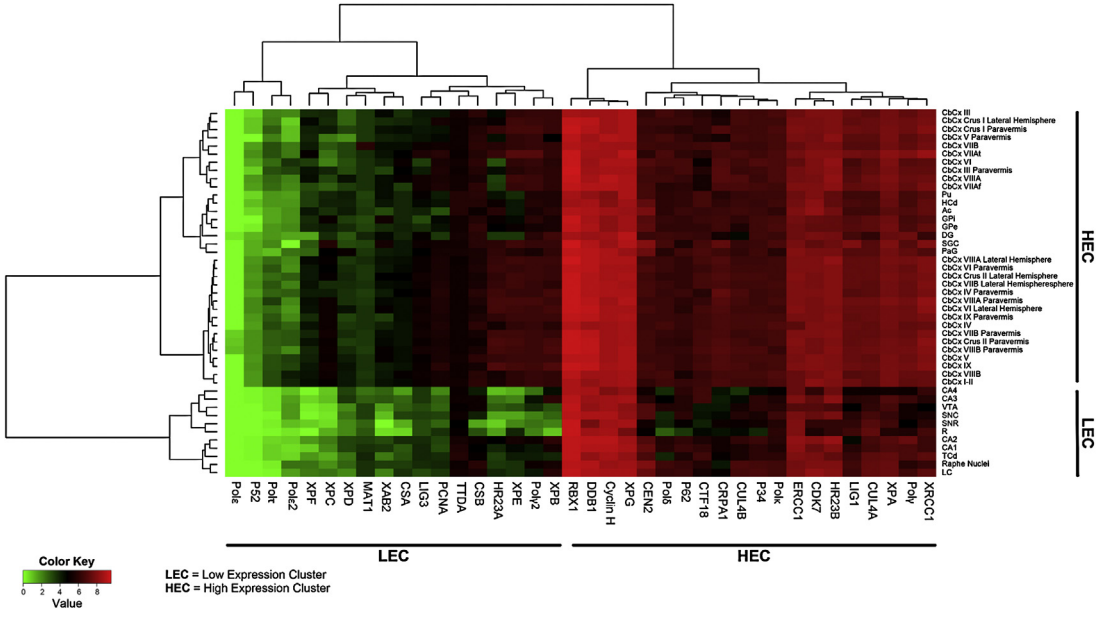

Fig. 2. Heat map and two-way cluster analysis of transcription profile of NER/TCR genes in the human brain. Genes are on the horizontal axis, areas are on the vertical axis. We used normalized Agilent custom designed microarray data from one health brain (code H0351.2001) from the Allen Human Brain Atlas of the Allen Institute for Brain Science (http://human.brain-map.org/). Both genes and areas can be clustered in two major groups on the basis of the expression levels.

Table 2
List, nomenclature, and abbreviations of the anatomical brain areas considered in this review.

Gene ID	Gene symbol	Gene symbol in the manuscript
902	CCNH	Cyclin H
1022	CDK7	CDK7
1069	CETN2	CEN2
63922	CHTF18	CTF18
8451	CUL4A	CUL4A
8450	CUL4B	CUL4B
1642	DDB1	DDB1
1643	DDB2	XPE
2067	ERCC1	ERCC1
2068	ERCC2	XPD
2071	ERCC3	XPB
2072	ERCC4	XPF
2073	ERCC5	XPG
2074	ERCC6	CSB
1161	ERCC8	CSA
2965	GTF2H1	P62
2967	GTF2H3	P34
2968	GTF2H4	P52
404672	GTF2H5	TTDA
3978	LIG1	LIG1
3980	LIG3	LIG3
4331	MNAT1	MAT1
5111	PCNA	PCNA
10714	POLD3	Polδ
5426	POLE	Polε
5427	POLE2	Polε2
5428	POLG	Polγ
11232	POLG2	Polγ2
5429	POLH	Polη
51426	POLK	Polκ
5886	RAD23A	HR23A
5887	RAD23B	HR23B
9978	RBX1	RBX1
6117	RPA1	RPA1
56949	XAB2	XAB2
7507	XPA	XPA
7508	XPC	XPC
7515	XRCC1	XRCC1

Supranuclear Palsy [98]. This disorders is characterized by dysfunction in the brainstem region, including the *substantia nigra* and shares important clinical features with PD, including parkinsonism (OMIM® entry 610898, http://www.ncbi.nlm.nih.gov/omim). The association between polymorphism in a NER gene and the disease provides evidence that this pathway can be of great relevance in the pathogenesis of neurodegenerative diseases.

The genes involved in the local unwinding step – common to both GG- and TC-NER and presumably to the broader TCR pathway) – are evenly distributed between the two expression level clusters. Genes of the XPA complex, which includes XPA and RPA, belong to the high expression cluster; conversely, the XPB and XPD helicases are in the low expression cluster, while the core subunit of the TFIIH complex are evenly distributed among the two clusters. XPA and RPA, which are implicated in stabilizing the open pre-incision intermediate, are in the high expression category. The next step, during which the dual incision is performed, is carried out by the factors XPF, ERCC1, and XPG enrich the NER complex. While XPF is poorly expressed, both XPG and ERCC1 are expressed at high levels. This observation seems counterintuitive because ERCC1 acts in concert with XPF, and in the absence of this interaction ERCC1 is highly unstable. It known, however, that the ERCC1 protein is highly unstable and can be rapidly degraded [99] and thus it is tempting to speculate that this might be part of a regulation system in which XPF transcript is rapidly inducible upon damage and high levels of ERCC1 mRNA are maintained constitutively to ensure rapid NER response.

The major polymerase in the brain is pol β, which is not involved in the subsequent repair synthesis step of NER and is instead strongly engaged in BER. The involved isoforms polδ and polκ fall in the high expression cluster, while polε expression is extremely low and probably negligible. It is difficult to frame these observations in the current literature because the pattern of expression and activity of polymerases other than polβ in neurons is largely obscure. A recent report on primary cultures suggests that some activity attributable to polδ can be found in neurons [100], but additional investigation is certainly required to dissect this issue.

The final players in the NER reaction are ligases and XRCC1. Also in this case the distribution is spread among clusters, with LIG1 and XRCC1 in the high expression group, and LIG3 in the low expression one. A recent important report by Gao and coworkers provided critical insights on the role of ligases in the brain [101]. In this study, LIG3 has been demonstrated to be important in the quality control of mtDNA in the brain, independently from XRCC1. Intriguingly, the same study demonstrates that LIG3 is dispensable for nuclear DNA quality control. Targeted deletion of LIG3 in neurons leads to viable animals and therefore indicates that LIG3 is not fundamental for proper development of the brain. The authors, however, assume that these animals might nonetheless have compromised mtDNA and mitochondria. Because of the strong nexus between neurodegenerative diseases and mitochondrial function, it is tempting to speculate that LIG3 might play some role in the pathobiology of these disorders, especially in those neurons with high rates of oxidative metabolism, such as dopaminergic neurons [102]. This topic might therefore be of great relevance for PD. Gao and colleagues also provide evidence that LIG1 is the isoform repairing DNA lesions in quiescent cells and that performs part of the function previously ascribed to LIG3. The high expression levels of LIG1 in the brain might reflect an important and possibly essential role for this enzyme in this organ.

The anatomical areas can also be clustered into two groups depending upon the transcripts' expression levels. Interestingly, regions involved in the initial stages of AD and PD fall in the low expressing group (Fig. 2, lower portion). It is very tempting to speculate that decreased expression of NER/TCR factors might indeed result in decreased DNA repair capacity and this could contribute to the selective vulnerability of these cells.

In summary, the role of NER in the etio-pathology of chronic ND is a promising and expanding research area. The number of available studies is rather limited at present, yet the topic is rapidly gaining momentum. Several clinical and experimental observations indicate that NER process might have great relevance in ND pathogenesis and could eventually explain, at least in part, important factors such as the effects of aging on disease onset. Our preliminary evidence describing the expression profiling of NER/TCR factors in the brain also confirms the possibility that this mechanism acts in the anatomical areas affected in ND. These preliminary findings are in line with available data showing that targeted deletion of NER factors in the hippocampus leads to neuronal degeneration and will be eventually corroborated by additional experiments in which ablation will be focused on other areas relevant for ND. Future and more specific research efforts should determine the extent of overlap between the neuropathology observed in NER/TCR models and that typical of human ND. These studies will be essential to determine unambiguously the location of NER/TCR in the pathogenic cascade and to obtain conclusive evidence that NER/TCR alterations do belong to the pathobiology of these devastating disorders.

Conflict of interest statement

The authors declare no conflict of interest.

Acknowledgements

PGM is supported by a grant from the Netherlands Genomics Initiative (NGI/NWO 05040202), a Marie Curie grant (IRG 247918), and the CEREBRAD grant under the EU-FP7 framework (project number 295552). JHJH acknowledges financial support of the National Institute of Health (NIH)/National Institute of Aging (NIA) (1PO1 AG-17242-02), NIEHS (1UO1 ES011044), the Royal Academy of Arts and Sciences of the Netherlands (academia professorship) and a European Research Council Advanced Grant. The research leading to these results has received funding from the European Community's Seventh Framework Program (FP7/2007-2013) under grant agreement No. HEALTH-F2-2010-259893. PGM is grateful to Dr. Laurie H. Sanders for constructive discussion on the role of DNA damage in neurodegenerative diseases.

References

[1] K.H. Kraemer, N.J. Patronas, R. Schiffmann, B.P. Brooks, D. Tamura, J.J. DiGiovanna, Xeroderma pigmentosum, trichothiodystrophy and Cockayne syndrome: a complex genotype–phenotype relationship, Neuroscience 145 (2007) 1388–1396.
[2] L.J. Niedernhofer, G.A. Garinis, A. Raams, A.S. Lalai, A.R. Robinson, E. Appeldoorn, H. Odijk, R. Oostendorp, A. Ahmad, W. van Leeuwen, A.F. Theil, W. Vermeulen, G.T. van der Horst, P. Meinecke, W.J. Kleijer, J. Vijg, N.G. Jaspers, J.H. Hoeijmakers, A new progeroid syndrome reveals that genotoxic stress suppresses the somatotroph axis, Nature 444 (2006) 1038–1043.
[3] M. Fousteri, L.H. Mullenders, Transcription-coupled nucleotide excision repair in mammalian cells: molecular mechanisms and biological effects, Cell Res. 18 (2008) 73–84.
[4] S.C. Shuck, E.A. Short, J.J. Turchi, Eukaryotic nucleotide excision repair: from understanding mechanisms to influencing biology, Cell Res. 18 (2008) 64–72.
[5] A.H. Sarker, S.E. Tsutakawa, S. Kostek, C. Ng, D.S. Shin, M. Peris, E. Campeau, J.A. Tainer, E. Nogales, P.K. Cooper, Recognition of RNA polymerase II and transcription bubbles by XPG, CSB, and TFIIH: insights for transcription-coupled repair and Cockayne Syndrome, Mol. Cell 20 (2005) 187–198.
[6] S.E. Tsutakawa, P.K. Cooper, Transcription-coupled repair of oxidative DNA damage in human cells: mechanisms and consequences, Cold Spring Harb. Symp. Quant. Biol. 65 (2000) 201–215.
[7] D.K. Jeppesen, V.A. Bohr, T. Stevnsner, DNA repair deficiency in neurodegeneration, Prog. Neurobiol. 94 (2011) 166–200.
[8] K. Sugasawa, UV-induced ubiquitylation of XPC complex, the UV-DDB-ubiquitin ligase complex, and DNA repair, J. Mol. Histol. 37 (2006) 189–202.
[9] M. Araki, C. Masutani, M. Takemura, A. Uchida, K. Sugasawa, J. Kondoh, Y. Ohkuma, F. Hanaoka, Centrosome protein centrin 2/caltractin 1 is part of the xeroderma pigmentosum group C complex that initiates global genome nucleotide excision repair, J. Biol. Chem. 276 (2001) 18665–18672.
[10] F. Bedez, B. Linard, X. Brochet, R. Ripp, J.D. Thompson, D. Moras, O. Lecompte, O. Poch, Functional insights into the core-TFIIH from a comparative survey, Genomics 101 (2013) 178–186.
[11] S. Ito, I. Kuraoka, P. Chymkowitch, E. Compe, A. Takedachi, C. Ishigami, F. Coin, J.M. Egly, K. Tanaka, XPG stabilizes TFIIH, allowing transactivation of nuclear receptors: implications for Cockayne syndrome in XP-G/CS patients, Mol. Cell 26 (2007) 231–243.
[12] G.S. Winkler, S.J. Araujo, U. Fiedler, W. Vermeulen, F. Coin, J.M. Egly, J.H. Hoeijmakers, R.D. Wood, H.T. Timmers, G. Weeda, TFIIH with inactive XPD helicase functions in transcription initiation but is defective in DNA repair, J. Biol. Chem. 275 (2000) 4258–4266.
[13] M. Missura, T. Buterin, R. Hindges, U. Hubscher, J. Kasparkova, V. Brabec, H. Naegeli, Double-check probing of DNA bending and unwinding by XPA-RPA: an architectural function in DNA repair, EMBO J. 20 (2001) 3554–3564.
[14] S.M. Patrick, J.J. Turchi, Xeroderma pigmentosum complementation group A protein (XPA) modulates RPA-DNA interactions via enhanced complex stability and inhibition of strand separation activity, J. Biol. Chem. 277 (2002) 16096–16101.
[15] L. Staresincic, A.F. Fagbemi, J.H. Enzlin, A.M. Gourdin, N. Wijgers, I. Dunand-Sauthier, G. Giglia-Mari, S.G. Clarkson, W. Vermeulen, O.D. Scharer, Coordination of dual incision and repair synthesis in human nucleotide excision repair, EMBO J. 28 (2009) 1111–1120.
[16] T. Ogi, S. Limsirichaikul, R.M. Overmeer, M. Volker, K. Takenaka, R. Cloney, Y. Nakazawa, A. Niimi, Y. Miki, N.G. Jaspers, L.H. Mullenders, S. Yamashita, M.I. Fousteri, A.R. Lehmann, Three DNA polymerases, recruited by different mechanisms, carry out NER repair synthesis in human cells, Mol. Cell 37 (2010) 714–727.
[17] J. Moser, H. Kool, I. Giakzidis, K. Caldecott, L.H. Mullenders, M.I. Fousteri, Sealing of chromosomal DNA nicks during nucleotide excision repair requires XRCC1 and DNA ligase III alpha in a cell-cycle-specific manner, Mol. Cell 27 (2007) 311–323.
[18] J.P. Laine, J.M. Egly, When transcription and repair meet: a complex system, Trends Genet. 22 (2006) 430–436.
[19] L.J. Niedernhofer, Nucleotide excision repair deficient mouse models and neurological disease, DNA repair 7 (2008) 1180–1189.
[20] H. Braak, I. Alafuzoff, T. Arzberger, H. Kretzschmar, K. Del Tredici, Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry, Acta Neuropathol. (Berl.) 112 (2006) 389–404.
[21] H. Braak, E. Braak, Pathoanatomy of Parkinson's disease, J. Neurol. 247 (Suppl. 2) (2000) II3–II10.
[22] R.J. Ferrante, N.W. Kowall, M.F. Beal, E.P. Richardson, E.D. Bird, J.B. Martin, Selective sparing of a class of striatal neurons in Huntington's disease, Science (New York, NY) 230 (1985) 561–563.
[23] E. Hirsch, A.M. Graybiel, Y.A. Agid, Melanized dopaminergic neurons are differentially susceptible to degeneration in Parkinson's disease, Nature 334 (1988) 345–348.
[24] M. Gleichmann, M.P. Mattson, Neuronal calcium homeostasis and dysregulation, Antioxid. Redox Signal. 14 (2011) 1261–1273.
[25] M.T. Lin, M.F. Beal, Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases, Nature 443 (2006) 787–795.
[26] A. Yamamoto, A. Simonsen, The elimination of accumulated and aggregated proteins: a role for aggrephagy in neurodegeneration, Neurobiol. Dis. 43 (2011) 17–28.
[27] J. Li, X. Ma, W. Yu, Z. Lou, D. Mu, Y. Wang, B. Shen, S. Qi, Reperfusion promotes mitochondrial dysfunction following focal cerebral ischemia in rats, PLoS ONE 7 (2012) e46498.
[28] Z.V. Niatsetskaya, S.A. Sosunov, D. Matsiukevich, I.V. Utkina-Sosunova, V.I. Ratner, A.A. Starkov, V.S. Ten, The oxygen free radicals originating from mitochondrial complex I contribute to oxidative brain injury following hypoxia–ischemia in neonatal mice, J. Neurosci. 32 (2012) 3235–3244.
[29] H. Chen, G.S. Kim, N. Okami, P. Narasimhan, P.H. Chan, NADPH oxidase is involved in post-ischemic brain inflammation, Neurobiol. Dis. 42 (2011) 341–348.
[30] I. Benilova, E. Karran, B. De Strooper, The toxic Abeta oligomer and Alzheimer's disease: an emperor in need of clothes, Nat. Neurosci. 15 (2012) 349–357.
[31] J.R. Cannon, J.T. Greenamyre, The role of environmental exposures in neurodegeneration and neurodegenerative diseases, Toxicol. Sci. 124 (2011) 225–250.
[32] A. Martinez, M. Portero-Otin, R. Pamplona, I. Ferrer, Protein targets of oxidative damage in human neurodegenerative diseases with abnormal protein aggregates, Brain Pathol. 20 (2010) 281–297.
[33] M. Pinto, A.M. Pickrell, C.T. Moraes, Regional susceptibilities to mitochondrial dysfunctions in the CNS, Biol. Chem. 393 (2012) 275–281.
[34] T. Tsunemi, A.R. La Spada, PGC-1alpha at the intersection of bioenergetics regulation and neuron function: from Huntington's disease to Parkinson's disease and beyond, Prog. Neurobiol. 97 (2012) 142–151.
[35] G.G. Glenner, C.W. Wong, Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein, Biochem. Biophys. Res. Commun. 120 (1984) 885–890.
[36] J.P. Guo, T. Arai, J. Miklossy, P.L. McGeer, Abeta and tau form soluble complexes that may promote self aggregation of both into the insoluble forms observed in Alzheimer's disease, Proc. Natl. Acad. Sci. U.S.A. 103 (2006) 1953–1958.
[37] A. Delacourte, N. Sergeant, D. Champain, A. Wattez, C.A. Maurage, F. Lebert, F. Pasquier, J.P. David, Nonoverlapping but synergetic tau and APP pathologies in sporadic Alzheimer's disease, Neurology 59 (2002) 398–407.
[38] E. Braak, H. Braak, Alzheimer's disease: transiently developing dendritic changes in pyramidal cells of sector CA1 of the Ammon's horn, Acta Neuropathol. (Berl.) 93 (1997) 323–325.
[39] H. Braak, E. Braak, Staging of Alzheimer's disease-related neurofibrillary changes, Neurobiol. Aging 16 (1995) 271–284.
[40] H. Braak, E. Braak, Diagnostic criteria for neuropathologic assessment of Alzheimer's disease, Neurobiol. Aging 18 (1997) S85–S88.
[41] T. Gasser, J. Hardy, Y. Mizuno, Milestones in PD genetics, Mov. Disord. 26 (2011) 1042–1048.
[42] D. Aarsland, L. Marsh, A. Schrag, Neuropsychiatric symptoms in Parkinson's disease, Mov. Disord. 24 (2009) 2175–2186.
[43] K.A. Jellinger, Neuropathology of sporadic Parkinson's disease: evaluation and changes of concepts, Mov. Disord. 27 (2012) 8–30.
[44] J.N. Guzman, J. Sanchez-Padilla, D. Wokosin, J. Kondapalli, E. Ilijic, P.T. Schumacker, D.J. Surmeier, Oxidant stress evoked by pacemaking in dopaminergic neurons is attenuated by DJ-1, Nature 468 (2010) 696–700.
[45] H. Braak, K. Del Tredici, U. Rub, R.A. de Vos, E.N. Jansen Steur, E. Braak, Staging of brain pathology related to sporadic Parkinson's disease, Neurobiol. Aging 24 (2003) 197–211.
[46] P.G. Mastroberardino, M. Piacentini, Type 2 transglutaminase in Huntington's disease: a double-edged sword with clinical potential, J. Intern. Med. 268 (2010) 419–431.
[47] S.E. Folstein, Huntington's disease: a disorder of families, in the John Hopkins series in contemporary medicine and public health, John Hopkins University Press, 1989, pp. 251.
[48] M. DiFiglia, E. Sapp, K.O. Chase, S.W. Davies, G.P. Bates, J.P. Vonsattel, N. Aronin, Aggregation of huntingtin in neuronal intranuclear inclusions and dystrophic neurites in brain, Science (New York, NY) 277 (1997) 1990–1993.
[49] P.G. Mastroberardino, C. Iannicola, R. Nardacci, F. Bernassola, V. De Laurenzi, G. Melino, S. Moreno, F. Pavone, S. Oliverio, L. Fesus, M. Piacentini, 'Tissue' transglutaminase ablation reduces neuronal death and prolongs survival in a mouse model of Huntington's disease, Cell Death Differ. 9 (2002) 873–880.

[50] R.J. Ferrante, M.F. Beal, N.W. Kowall, E.P. Richardson, J.B. Martin, Sparing of acetylcholinesterase-containing striatal neurons in Huntington's disease, Brain Res. 411 (1987) 162–166.
[51] D. Joel, Open interconnected model of basal ganglia-thalamocortical circuitry and its relevance to the clinical syndrome of Huntington's disease, Mov. Disord. 16 (2001) 407–423.
[52] L. Weissman, N.C. de Souza-Pinto, T. Stevnsner, V.A. Bohr, DNA repair, mitochondria, and neurodegeneration, Neuroscience 145 (2007) 1318–1329.
[53] I. Mellon, Transcription-coupled repair: a complex affair, Mutat. Res. 577 (2005) 155–161.
[54] T. Nouspikel, DNA repair in differentiated cells: some new answers to old questions, Neuroscience 145 (2007) 1213–1221.
[55] D. Jaarsma, I. Van Der Pluijm, M. De Waard, E. Haasdijk, R. Brandt, M. Vermeij, Y. Rijksen, A. Maas, H. Van Steeg, J.H. Hoeijmakers, G.T. van der Horst, Age-related neuronal degeneration: complementary roles of nucleotide excision repair and transcription-coupled repair in preventing neuropathology, PLoS Genet. 7 (2011) e1002405.
[56] I. Rapin, K. Weidenheim, Y. Lindenbaum, P. Rosenbaum, S.N. Merchant, S. Krishna, D.W. Dickson, Cockayne syndrome in adults: review with clinical and pathologic study of a new case, J. Child Neurol. 21 (2006) 991–1006.
[57] N.J. Lawrence, J.J. Sacco, D.G. Brownstein, T.H. Gillingwater, D.W. Melton, A neurological phenotype in mice with DNA repair gene Ercc1 deficiency, DNA repair 7 (2008) 281–291.
[58] G. Weeda, I. Donker, J. de Wit, H. Morreau, R. Janssens, C.J. Vissers, A. Nigg, H. van Steeg, D. Bootsma, J.H. Hoeijmakers, Disruption of mouse ERCC1 results in a novel repair syndrome with growth failure, nuclear abnormalities and senescence, Curr. Biol. 7 (1997) 427–439.
[59] N.Z. Borgesius, M.C. de Waard, I. Van Der Pluijm, A. Omrani, G.C. Zondag, G.T. van der Horst, D.W. Melton, J.H. Hoeijmakers, D. Jaarsma, Y. Elgersma, Accelerated age-related cognitive decline and neurodegeneration, caused by deficient DNA repair, J. Neurosci. 31 (2011) 12543–12553.
[60] J.S. Jacobsen, C.C. Wu, J.M. Redwine, T.A. Comery, R. Arias, M. Bowlby, R. Martone, J.H. Morrison, M.N. Pangalos, P.H. Reinhart, F.E. Bloom, Early-onset behavioral and synaptic deficits in a mouse model of Alzheimer's disease, Proc. Natl. Acad. Sci. U.S.A. 103 (2006) 5161–5166.
[61] S.N. Burke, C.A. Barnes, Neural plasticity in the ageing brain, Nat. Rev. Neurosci. 7 (2006) 30–40.
[62] B.A. Yankner, T. Lu, P. Loerch, The aging brain, Annu. Rev. Pathol. 3 (2008) 41–66.
[63] G.M. Halliday, C.H. Stevens, Glia: initiators and progressors of pathology in Parkinson's disease, Mov. Disord. 26 (2011) 6–17.
[64] V. Parpura, M.T. Heneka, V. Montana, S.H. Oliet, A. Schousboe, P.G. Haydon, R.F. Stout Jr., D.C. Spray, A. Reichenbach, T. Pannicke, M. Pekny, M. Pekna, R. Zorec, A. Verkhratsky, Glial cells in (patho)physiology, J. Neurochem. 121 (2012) 4–27.
[65] A. Aguzzi, B.A. Barres, M.L. Bennett, Microglia: scapegoat, saboteur, or something else? Science 339 (2013) 156–161.
[66] S. Fernandez-Fernandez, A. Almeida, J.P. Bolanos, Antioxidant and bioenergetic coupling between neurons and astrocytes, Biochem. J. 443 (2012) 3–11.
[67] S.Z. Yang, Y.F. Zhang, L.M. Zhang, Y.L. Huang, F.Y. Sun, Immunohistochemical analysis of nucleotide excision repair factors XPA and XPB in adult rat brain, Anat. Rec. 291 (2008) 775–780 (Hoboken, NJ: 2007).
[68] A. Yamamoto, Y. Nakamura, N. Kobayashi, T. Iwamoto, A. Yoshioka, H. Kuniyasu, T. Kishimoto, T. Mori, Neurons and astrocytes exhibit lower activities of global genome nucleotide excision repair than do fibroblasts, DNA repair 6 (2007) 649–657.
[69] S.C. Smith, A.R. Robinson, L. Niedernhofer, M. Hetman, Downregulation of cholesterol biosynthesis genes in the forebrain of ERCC1-deficient mice, Neurobiol. Dis. 45 (2012) 1136–1144.
[70] G. Bu, Apolipoprotein E and its receptors in Alzheimer's disease: pathways, pathogenesis and therapy, Nat. Rev. Neurosci. 10 (2009) 333–344.
[71] P. Gamba, G. Testa, B. Sottero, S. Gargiulo, G. Poli, G. Leonarduzzi, The link between altered cholesterol metabolism and Alzheimer's disease, Ann. N.Y. Acad. Sci. 1259 (2012) 54–64.
[72] K. Usui, J.D. Hulleman, J.F. Paulsson, S.J. Siegel, E.T. Powers, J.W. Kelly, Site-specific modification of Alzheimer's peptides by cholesterol oxidation products enhances aggregation energetics and neurotoxicity, Proc. Natl. Acad. Sci. U.S.A. 106 (2009) 18563–18568.
[73] N.E. Shepardson, G.M. Shankar, D.J. Selkoe, Cholesterol level and statin use in Alzheimer disease: I. Review of epidemiological and preclinical studies, Arch. Neurol. 68 (2011) 1239–1244.
[74] M. Valenza, E. Cattaneo, Emerging roles for cholesterol in Huntington's disease, Trends Neurosci. 34 (2011) 474–486.
[75] M.C. de Waard, I. Van Der Pluijm, N. Zuiderveen Borgesius, L.H. Comley, E. Haasdijk, Y. Rijksen, Y. Ridwan, G. Zondag, J.H. Hoeijmakers, Y. Elgersma, T.H. Gillingwater, D. Jaarsma, Age-related motor neuron degeneration in DNA repair-deficient Ercc1 mice, Acta Neuropathol. (Berl.) 120 (2010) 461–475.
[76] A.T. Sands, A. Abuin, A. Sanchez, C.J. Conti, A. Bradley, High susceptibility to ultraviolet-induced carcinogenesis in mice lacking XPC, Nature 377 (1995) 162–165.
[77] D.L. Cheo, H.J. Ruven, L.B. Meira, R.E. Hammer, D.K. Burns, N.J. Tappe, A.A. van Zeeland, L.H. Mullenders, E.C. Friedberg, Characterization of defective nucleotide excision repair in XPC mutant mice, Mutat. Res. 374 (1997) 1–9.
[78] A. de Vries, C.T. van Oostrom, F.M. Hofhuis, P.M. Dortant, R.J. Berg, F.R. de Gruijl, P.W. Wester, C.F. van Kreijl, P.J. Capel, H. van Steeg, S.J. Verbeek, Increased susceptibility to ultraviolet-B and carcinogens of mice lacking the DNA excision repair gene XPA, Nature 377 (1995) 169–173.
[79] L.A. Bindoff, M. Birch-Machin, N.E. Cartlidge, W.D. Parker, D.M. Turnbull, Mitochondrial function in Parkinson's disease, Lancet 2 (1989) 49.
[80] M. Gu, M.T. Gash, V.M. Mann, F. Javoy-Agid, J.M. Cooper, A.H. Schapira, Mitochondrial defect in Huntington's disease caudate nucleus, Ann. Neurol. 39 (1996) 385–389.
[81] W.D. Parker, S.J. Boyson, J.K. Parks, Abnormalities of the electron transport chain in idiopathic Parkinson's disease, Ann. Neurol. 26 (1989) 719–723.
[82] W.D. Parker, N.J. Mahr, C.M. Filley, J.K. Parks, D. Hughes, D.A. Young, C.M. Cullum, Reduced platelet cytochrome c oxidase activity in Alzheimer's disease, Neurology 44 (1994) 1086–1090.
[83] W.D. Parker, J. Parks, C.M. Filley, B.K. Kleinschmidt-DeMasters, Electron transport chain defects in Alzheimer's disease brain, Neurology 44 (1994) 1090–1096.
[84] M.P. Horowitz, C. Milanese, R. Di Maio, X. Hu, L.M. Montero, L.H. Sanders, V. Tapias, S. Sepe, W.A. van Cappellen, E.A. Burton, J.T. Greenamyre, P.G. Mastroberardino, Single-cell redox imaging demonstrates a distinctive response of dopaminergic neurons to oxidative insults, Antioxid. Redox Signal. 15 (2011) 855–871.
[85] P.G. Mastroberardino, A.L. Orr, X. Hu, H.M. Na, J.T. Greenamyre, A FRET-based method to study protein thiol oxidation in histological preparations, Free Radic. Biol. Med. 45 (2008) 971–981.
[86] A.M. Cuervo, E.S. Wong, M. Martinez-Vicente, Protein degradation, aggregation, and misfolding, Mov. Disord. 25 (Suppl. 1) (2010) S49–S54.
[87] I. Magen, M.F. Chesselet, Genetic mouse models of Parkinson's disease. The state of the art, Prog. Brain Res. 184 (2010) 53–87.
[88] K. Hsiao, P. Chapman, S. Nilsen, C. Eckman, Y. Harigaya, S. Younkin, F. Yang, G. Cole, Correlative memory deficits, Abeta elevation, and amyloid plaques in transgenic mice, Science (New York, NY) 274 (1996) 99–102.
[89] S. Ramaswamy, J.L. McBride, J.H. Kordower, Animal models of Huntington's disease, ILAR J. 48 (2007) 356–373.
[90] V.C. Wheeler, W. Auerbach, J.K. White, J. Srinidhi, A. Auerbach, A. Ryan, M.P. Duyao, V. Vrbanac, M. Weaver, J.F. Gusella, A.L. Joyner, M.E. MacDonald, Length-dependent gametic CAG repeat instability in the Huntington's disease knock-in mouse, Hum. Mol. Genet. 8 (1999) 115–122.
[91] V.C. Wheeler, J.K. White, C.A. Gutekunst, V. Vrbanac, M. Weaver, X.J. Li, S.H. Li, H. Yi, J.P. Vonsattel, J.F. Gusella, S. Hersch, W. Auerbach, A.L. Joyner, M.E. MacDonald, Long glutamine tracts cause nuclear localization of a novel form of huntingtin in medium spiny striatal neurons in HdhQ92 and HdhQ111 knock-in mice, Hum. Mol. Genet. 9 (2000) 503–513.
[92] E.K. Richfield, M.J. Thiruchelvam, D.A. Cory-Slechta, C. Wuertzer, R.R. Gainetdinov, M.G. Caron, D. Di Monte, H.J. Federoff, Behavioral and neurochemical effects of wild-type and mutated human alpha-synuclein in transgenic mice, Exp. Neurol. 175 (2002) 35–48.
[93] R.M. Miller, G.L. Kiser, T. Kaysser-Kranich, C. Casaceli, E. Colla, M.K. Lee, C. Palaniappan, H.J. Federoff, Wild-type and mutant alpha-synuclein induce a multi-component gene expression profile consistent with shared pathophysiology in different transgenic mouse models of PD, Exp. Neurol. 204 (2007) 421–432.
[94] M.J. Hawrylycz, E.S. Lein, A.L. Guillozet-Bongaarts, E.H. Shen, L. Ng, J.A. Miller, L.N. van de Lagemaat, K.A. Smith, A. Ebbert, Z.L. Riley, C. Abajian, C.F. Beckmann, A. Bernard, D. Bertagnolli, A.F. Boe, P.M. Cartagena, M.M. Chakravarty, M. Chapin, J. Chong, R.A. Dalley, B.D. Daly, C. Dang, S. Datta, N. Dee, T.A. Dolbeare, V. Faber, D. Feng, D.R. Fowler, J. Goldy, B.W. Gregor, Z. Haradon, D.R. Haynor, J.G. Hohmann, S. Horvath, R.E. Howard, A. Jeromin, J.M. Jochim, M. Kinnunen, C. Lau, E.T. Lazarz, C. Lee, T.A. Lemon, L. Li, Y. Li, J.A. Morris, C.C. Overly, P.D. Parker, S.E. Parry, M. Reding, J.J. Royall, J. Schulkin, P.A. Sequeira, C.R. Slaughterbeck, S.C. Smith, A.J. Sodt, S.M. Sunkin, B.E. Swanson, M.P. Vawter, D. Williams, P. Wohnoutka, H.R. Zielke, D.H. Geschwind, P.R. Hof, S.M. Smith, C. Koch, S.G. Grant, A.R. Jones, An anatomically comprehensive atlas of the adult human brain transcriptome, Nature 489 (2012) 391–399.
[95] J.M. Ng, W. Vermeulen, G.T. van der Horst, S. Bergink, K. Sugasawa, H. Vrieling, J.H. Hoeijmakers, A novel regulation mechanism of DNA repair by damage-induced and RAD23-dependent stabilization of xeroderma pigmentosum group C protein, Genes Dev. 17 (2003) 1630–1645.
[96] G.T. van der Horst, L. Meira, T.G. Gorgels, J. De Wit, S. Velasco-Miguel, J.A. Richardson, Y. Kamp, M.P. Vreeswijk, B. Smit, D. Bootsma, J.H. Hoeijmakers, E.C. Friedberg, UVB radiation-induced cancer predisposition in Cockayne syndrome group A (Csa) mutant mice, DNA Repair 1 (2002) 143–157.
[97] G.T. van der Horst, H. van Steeg, R.J. Berg, A.J. van Gool, J. de Wit, G. Weeda, H. Morreau, R.B. Beems, C.F. van Kreijl, F.R. de Gruijl, D. Bootsma, J.H. Hoeijmakers, Defective transcription-coupled repair in Cockayne syndrome B mice is associated with skin cancer predisposition, Cell 89 (1997) 425–435.
[98] S. Melquist, D.W. Craig, M.J. Huentelman, R. Crook, J.V. Pearson, M. Baker, V.L. Zismann, J. Gass, J. Adamson, S. Szelinger, J. Corneveaux, A. Cannon, K.D. Coon, S. Lincoln, C. Adler, P. Tuite, D.B. Calne, E.H. Bigio, R.J. Uitti, Z.K. Wszolek, L.I. Golbe, R.J. Caselli, N. Graff-Radford, I. Litvan, M.J. Farrer, D.W. Dickson, M. Hutton, D.A. Stephan, Identification of a novel risk locus for progressive supranuclear palsy by a pooled genomewide scan of 500,288 single-nucleotide polymorphisms, Am. J. Hum. Genet. 80 (2007) 769–778.
[99] A.M. Sijbers, P.J. van der Spek, H. Odijk, J. van den Berg, M. van Duin, A. Westerveld, N.G. Jaspers, D. Bootsma, J.H. Hoeijmakers, Mutational analysis of the

human nucleotide excision repair gene ERCC1, Nucleic Acids Res. 24 (1996) 3370–3380.
[100] N.S. Raji, T.H. Krishna, K.S. Rao, DNA-polymerase alpha, beta, delta and epsilon activities in isolated neuronal and astroglial cell fractions from developing and aging rat cerebral cortex, Int. J. Dev. Neurosci. 20 (2002) 491–496.
[101] Y. Gao, S. Katyal, Y. Lee, J. Zhao, J.E. Rehg, H.R. Russell, P.J. McKinnon, DNA ligase III is critical for mtDNA integrity but not Xrcc1-mediated nuclear DNA repair, Nature 471 (2011) 240–244.
[102] C.S. Chan, T.S. Gertler, D.J. Surmeier, A molecular basis for the increased vulnerability of substantia nigra dopamine neurons in aging and Parkinson's disease, Mov. Disord. 25 (Suppl 1) (2010) S63–S70.
[103] M.M. Lewis, G. Du, M. Kidacki, N. Patel, M.L. Shaffer, R.B. Mailman, X. Huang, Higher iron in the red nucleus marks Parkinson's dyskinesia, Neurobiol. Aging (2012).
[104] M.E. Colpan, K.V. Slavin, Subthalamic and red nucleus volumes in patients with Parkinson's disease: do they change with disease progression? Parkinsonism Relat. Disord. 16 (2010) 398–403.
[105] R.L. Doty, Olfactory dysfunction in Parkinson disease, Nat. Rev. Neurol. 8 (2012) 329–339.
[106] L.T. Grinberg, U. Rueb, A.T. Alho, H. Heinsen, Brainstem pathology and non-motor symptoms in PD, J. Neurol. Sci. 289 (2010) 81–88.