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The role of the DNA damage response in neuronal development, organization and maintenance

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ABSTRACT

The DNA damage response is a key factor in the maintenance of genome stability. As such, it is a central axis in sustaining cellular homeostasis in a variety of contexts: development, growth, differentiation, and maintenance of the normal life cycle of the cell. It is now clear that diverse mechanisms encompassing cell cycle regulation, repair pathways, many aspects of cellular metabolism, and cell death are inter-linked and act in consort in response to DNA damage. Defects in the DNA damage response in proliferating cells can lead to cancer while defects in neurons result in neurodegenerative pathologies. Neurons are highly differentiated, post-mitotic cells that cannot be replenished after disease or trauma. Their high metabolic activity that generates large amounts of reactive oxygen species with DNA damaging capacity and their intense transcriptional activity increase the potential for damage of their genomic DNA. Neurons ensure their longevity and functionality in the face of these threats by elaborate mechanisms that defend the integrity of their genome. This review focuses on the DNA damage response in neuronal cells and points to the importance of this elaborate network to the integrity of the nervous system from its early development and throughout the lifetime of the organism.

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1. Introduction: neurons and the DNA damage response

Neurons are unique among our myriad types of cells. They are terminally differentiated, post-mitotic cells, yet are extremely active. Since they are irreplaceable and should survive as long as the organism does, they need elaborate, stringent defense mechanisms to ensure their longevity. Neurons display high rates of transcription and translation, which are associated with high rates of metabolism and mitochondrial activity. The amount of oxygen consumed by the brain relative to its size far exceeds that of other organs. This high activity coupled with high oxygen consumption creates a stressful environment for neurons: damaging metabolic by-products, primarily reactive oxygen species (ROS), are constantly attacking neuronal genomic and mitochondrial DNA [1–7].

The cellular defense system against this threat is the DNA damage response (DDR) – an elaborate signaling network activated by DNA damage that swiftly modulates many physiological processes [8–11]. Genetic defects in critical relays in this network lead to genomic instability syndromes, which are almost invariably characterized by degeneration of specific tissues, sensitivity to specific DNA-damaging agents, chromosomal instability, and a marked predisposition to cancer [12,13]. A wealth of information has been accumulated on this system on commonly used cancer cell lines [14,15].

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One of the most powerful activators of the DDR is the double strand break (DSB) in the DNA [16]. Eukaryotic cells employ two major mechanisms to repair DSBs: nonhomologous end-joining (NHEJ), an error-prone ligation mechanism, and a high-fidelity process based on homologous recombination (HR) between sister chromatids that operates in the late S and G2 phases of the cell cycle [17,18]. But, the overall cellular response to DSBs goes far beyond repair. This broad, powerful signaling network works swiftly and vigorously to affect chromatin organization and a large number of cellular systems [9,11,14,20,21]. One of its hallmarks in proliferating cells is the activation of cell cycle checkpoints that temporarily halt the cell cycle while damage is assessed and processed [9,14,15,22,23].

The DSB response is a multi-tiered process that begins with rapid recruitment to the break sites of early damage response proteins (commonly dubbed "sensors"), which create expanding nuclear foci at these sites. Among them are the MRE11/RAD50/NBS1 (MRN) complex [24,25], the tumor suppressor protein BRCA1 [26], the p53-binding protein 53BP1 [27,28], MDC1 [28–30], RNF8 [31–34], RAP80 [34–38] and Abraxas [37]. These proteins participate in initial processing of the damage and gradually build up a signaling cascade that leads to the activation of the *transducers* [28,39–44]. The primary transducer of the DSB alarm is the nuclear serine-threonine kinase ATM [11,20,25,45]. In response to DSB induction, inert ATM is rapidly activated while undergoing several post-translational modifications [46–49], and a portion of activated ATM is recruited to the DSB sites [50–53]. ATM then phosphorylates a plethora of effectors, which are players in a variety of damage response pathways [20,25,54–56]. ATM belongs to a conserved family of "PI3K-like protein kinases" (PIKKs) [57], which includes among others two other major DDR transducers, the DNA-dependent protein kinase (DNA-PK), which is involved in the NHEJ repair pathway [58], and ATR (ataxia-telangiectasia and Rad3-related) [59]. ATR is activated primarily by single stranded DNA stretches formed during DSB and UV damage processing and stalled replication forks, and thus responds DSBs later and with slower kinetics compared to ATM. While ATM and ATR share substrates in the DSB response, they exhibit selective substrate specificities in response to different genotoxic stresses and different DSB inducers, and evidence is emerging for a close cross-talk between these two major transducers [59–62]. An important substrate of ATM, ATR, and DNA-PK in the vicinity of the damaged site is the histone H2AX, which represents a sub-family of histone H2A. Phosphorylation of H2AX spreads rapidly over megabases of genomic DNA flanking the DSB, and phosphorylated H2AX (γH2AX) plays an important role in anchoring damage response proteins to the damaged sites [30,63–68]. Since ATM phosphorylates some of the proteins that are required for its activation, the initial phase of the DNA damage response is no longer viewed as a simple hierarchy of "sensors upstream of transducers", but rather as a cyclic process that amplifies the damage signal via repeated interactions among these proteins [20,25,45]. This signal amplification depends on interaction of the sensors/activators with damaged chromatin on the one hand [64,69,70], and ATM on the other hand [20,25,30,45,52,71–73].

The DSB response activates one of two alternatives: a pro-survival network that includes the damage-induced cell cycle checkpoints, DSB repair, alterations in gene expression profiles, protein synthesis, degradation and trafficking, and RNA processing and nuclear export; or programmed cell death [74,75]. The mechanistic aspects of this critical choice remain elusive.

While most of the work to elucidate DDR components – especially those associated with cell survival – has been carried out in proliferating cell lines, it recently became evident that a proper DNA damage response is critically important for normal development and organization of the nervous system, as well as for its maintenance throughout the lifetime of the organism. Malfunction of the DNA damage response accelerates neuronal death and may lead to neurodegenerative processes.

2. Genetic defects in human and mouse, linking neuronal mal-development or neurodegeneration with defective DDR

2.1. *Human monogenic disorders*

The nervous system develops in a basic pattern of proliferation, differentiation, migration and maturation. It forms from proliferative ventricular zones that generate neural precursor cells. Two main classes of cells make up the nervous system, neurons and glia, and these encompass many specialized sub-types. As these cells exit the cell cycle, they migrate and differentiate, shaping the nervous system. The brain is probably the most elaborate and complex structure in mammalians. To generate a functional nervous system that will survive throughout the lifetime of the organism, numerous processes have to take place in a precise time- and space-controlled manner. Hence, a proper DDR is essential for neuronal development. Evidence of the connection between DNA damage and neurodegeneration is found in genetic disorders affecting the DDR, chronic neurodegenerative disorders, and studies of neurodevelopment and aging processes [2,5,76–81].

Several human monogenic defects affecting DDR pathways are characterized by neurological deficits [2,11,13,76,77,82–93] (Table 1 and Fig. 1; see also O'Driscoll and Jeggo, this volume). In this section emphasis will be put on those caused by deficiencies in DNA strand break repair, however, it should be mentioned that defects in nucleotide excision repair (NER) also lead to various degrees of neuronal damage [3,76,88,92–95] (see contributions by Nouspikel, Brooks, and Niedernhofer in this Volume). It has been suggested, however, that the NER deficiencies the DNA lesions that accumulate in neurons are in fact single strand breaks [93].

2.2. *Animal models linking DDR and neuronal development*

Over the years a large number of mouse mutant strains of DNA repair and other cellular responses to DNA damage components have been generated [96,97] (see also Niedernhofer, and Frappart and McKinnon in this volume). Many of them do not grossly exhibit the overt neurodegeneration seen in

Table 1 – Human monogenic neurodegenerative disorders associated with DDR defects

Syndrome	Affected protein and pathway	Affected brain area	Main neuronal implications	Non-neuronal symptoms	References
DSB response					
Ataxia telangiectasia (A-T)	ATM (activation of the DSB response)	Cerebellum; extrapyramidal movement system	Early onset of cerebellar ataxia degeneration of Purkinje and granule neurons; progressive ataxia; oculomotor deficits; dysarthria	Immunodeficiency; telangiectasia; radiosensitivity; lymphoid malignancy; sterility	[56,238–240]
A-T like disorder (A-TLD)	MRE11 (sensing and initial processing of DSBs; ATM activation)	Cerebellum	Late onset of cerebellar ataxia; degeneration of Purkinje and granule neurons; dysarthria; abnormal eye movement;	Radiosensitivity; chromosome fragility	[24,51–53,71–73,119,121,241–243]
Nijmegen breakage Syndrome (NBS)	NBS1 (MRN complex function; ATM recruitment; other, unknown pathways)	Cerebral cortex	Microcephaly; mental deficiency	Immunodeficiency; radiosensitivity; chromosome fragility; lymphoid malignancy	[11,245–248]
ATR Seckel syndrome (ATR-SS)	ATR; PCNT (ATR-mediated signaling)	Cerebral cortex	Microcephaly; mental deficiency	Growth retardation; skeletal abnormalities; dysmorphic facies	[249–253]
Primary microcephaly (PM)	MCPH1/BRIT	Cerebral cortex	Defective neurogenesis; mental retardation	Breast, ovarian and prostate cancer	[82,254–257]
Immunodeficiency with microcephaly	Cernunnos/XLF	Cerebral cortex	Microcephaly	Growth retardation; lymphopenia; cellular radiosensitivity	[258–265]
Ligase 4 syndrome	LIG4 (NHEJ pathway of DSB repair)	Cerebral cortex	Microcephaly; cognitive delay	Developmental and growth delay; immune deficiency; pancytopenia; dysmorphic facies; lymphoid tumors; cellular radiosensitivity	[89,266]
SSB response					
Ataxia with oculomotor apraxia (AOA1)	Aprataxin	Cerebellum; nigro-striatal pathway	Early onset ataxia; neurodegeneration (Purkinje neurons); oculomotor apraxia; dysarthria; limb dysmetria	Hypoalbuminemia; hypocholesterolemia	[76,90,172,173,267–279]
Ataxia-ocular apraxia 2 (AOA2)	Senataxin	Cerebellum spinal cord	Cerebellar atrophy; axonal sensorimotor neuropathy; oculomotor apraxia; dysarthria; distal amyotrophy	Elevated α-fetoprotein	[90,271,276,280–287]
Spinocerebellar ataxia with axonal neuropathy (SCAN1)	Tyrosyl-DNA phosphor-diesterase (TDP1)	Spinocerebellar pathway	Cerebellar ataxia; axonal sensorimotor neuropathy	Hypoalbuminemia; hypercholesterolemia	[76,173,272,288–294]
Nucleotide excision repair					
Xeroderma pigmentosum (XP) with neurological disease	XPA, XPD, XPG	Cerebrum	Sensorineural deafness; progressive neurodegeneration; cerebral and cerebellar atrophy; dysmyelination; calcification of basal ganglia (30% of patients)	Sunlight sensitivity; increased skin pigmentation; multiple skin lesions; skin cancer	[92,95,295–297]
Cockayne's syndrome (CS) and XP/CS	CSA, CSB, XPB, XPD, XPG	Cerebral cortex	Microcephaly; progressive neurodegeneration; cerebral and cerebellar atrophy; sensorineural deafness; dysmyelination	Growth retardation; sunlight sensitivity; congenital cataracts; progeric symptoms; immature sexual development	[92,297–300]
Trichothiodystrophy (TTD)	XPB, XPD TFB5/TTDA	Cerebral cortex	Microcephaly; hypomyelination; psychomotoric abnormalities	Brittle hair; sunlight sensitivity; short stature; developmental delay; congenital cataracts;	[92,297,301,302]

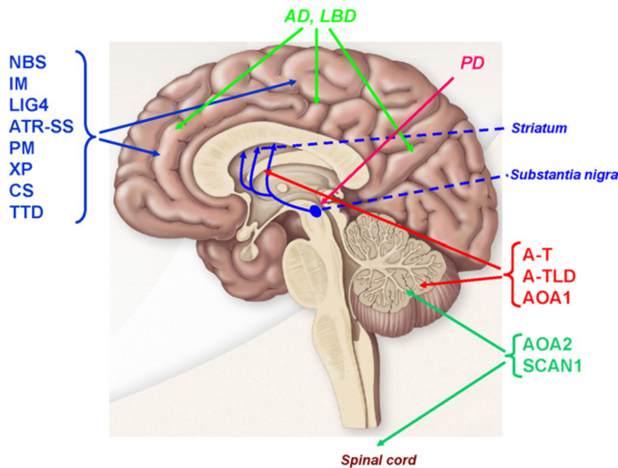

Fig. 1 – Schematic presentation of brain areas that are affected in DDR-associated neurodegenerative diseases. Primary DDR defects: ataxia-telangiectasia (A-T), ataxia-telangiectasia like disorder (A-TLD) and ataxia with oculomotor apraxia 1 (AOA1) affect mainly the cerebellum and the nigrostriatal pathway. Damage to the cerebral cortex is caused in patients with Nijmegen breakage syndrome (NBS), immunodeficiency with microcephaly (IM), ligase IV syndrome (LIG4), ATR Seckel syndrome (ATR-SS), xeroderma pigmentosum (XP), Cockayne syndrome (CS) and Trichothiodystrophy (TTD). Ataxia with oculomotor apraxia 2 (AOA2) and spinocerebellar ataxia with axonal neuropathy (SCAN1) lead to degeneration in the cerebellum and spinal cord. Late onset neurodegenerative disorders that show alterations in DDR capacity: Parkinson's disease (PD) leads to degeneration of dopaminergic neurons in the substantia nigra pars compacta; Alzheimer's disease (AD) and dementia with Lewy body disease (LBD) cause neuronal death primarily in the cerebral cortex (see also Tables 1 and 2).

human genetic diseases [83,96,98–101], but these models have produced compelling evidence of the importance of DNA damage processing in nervous system development. For example, disruption of one of two core proteins of the NHEJ repair pathway, XRCC4 or Ligase IV, resulted in embryonic lethality due to excessive apoptosis in the nervous system [102–105]. These models also showed the importance of the NHEJ for V(D)J recombination during immune system development since inactivation of XRCC4 and Ligase IV affected both the immune system and the nervous system [102–104,106].

There is an interesting hypothesis that during nervous system development, yet unrecognized DNA DSBs and DNA recombination occur physiologically, similar to the V(D)J recombination seen during the development of lymphocytes [106,107]. The possibility that neuronal genomes are cleaved and rejoined as part of neurogenesis could explain the extensive neuronal apoptosis that takes place in the normal developing brain, as it does in the immune system [106]. Inactivation of Ku70/Ku80, the accessory subunits of DNA-PK a key player in NHEJ [58], led to viable mice that still exhibited aberrant neural apoptosis qualitatively similar to, but less severe than, that associated with XRCC4 and Ligase IV [108]. Surprisingly, lack of a neuronal death phenotype in the viable DNA-PK catalytic subunit (DNA-PKcs) knockout mice was reported [108]. However, analysis of the nervous system in *SCID* mice, a mutant strain that expresses a truncated and enzymatically inactive form of DNA-PKcs, indicated elevated DSBs and apoptosis in the nervous system [109,110]. Nevertheless, *SCID* mice do not show a striking decrease in brain size or abnormal cytoarchitecture [109]. *Atm*-knockout mice were also an unexpected exception: while exhibiting most of the features of human A-T, they barely show the cerebellar degeneration and associated neuromotor dysfunction [98–100] (see also Biton et al., this volume). Immature *Atm*-deficient neurons in these mice were, however, resistant to DNA damage-induced apoptosis [111–113]. It has been suggested that in the developing nervous system, this resistance to apoptosis may result in incorporation of DNA damaged cells into the final form of the nervous system, and their subsequent dysfunction eventually accounts for the neurodegeneration [104,111,113–115]. Interestingly, differentiation status of neural cells is a critical determinant in the activation of certain apoptotic pathways; selective requirement for Atm in eliminating damaged post-mitotic neural cells was first reported by Lee et al. [115]. Furthermore, it was recently suggested that NHEJ is dispensable for a substantial portion of early nervous system development, during which DSB repair utilizes HR. While inactivation of Xrcc2, an HR component, resulted in DNA damage-induced apoptosis in proliferating neural precursors cells, inactivation of Ligase IV, which disrupts the NHEJ, mainly affected differentiating cells later in developmental [116]. During neurogenesis, DNA damage-induced apoptosis after disrupting NHEJ but not HR requires Atm [104,116,117]. Inactivation of downstream effectors of Atm signaling also abrogated the DNA damage-induced apoptosis in the nervous system [114,115].

The lack of neurodegeneration in Atm knockout mice [111–113] was disappointing, although a severe cerebellar phenotype combining the neurological anomalies of NBS, A-T and ATLD was obtained by conditionally knocking out the Nbs1 protein in the mouse nervous system [118]. The resulting animal model is a prime example of the interrelations between DDR and CNS development [118]. This mouse, Nbs1-CNS-del, exhibits microcephaly, growth retardation, proliferation arrest of the granule cell progenitors, and apoptosis of post-mitotic neurons in the cerebellum. Remarkably, depletion of p53 substantially rescued the neurological phenotype of this mouse [118]. This striking phenotype was explained by the requirement of the MRN complex for full activation of both ATM and ATR [44,51,52,119–121].

In a subsequent study, Yang et al. [122] found that targeted disruption of murine Nbs1 in the lens altered the nuclear localization of the MRN complex and resulted in microphthalmia due to reduced proliferation of the lens epithelial cells. Interestingly, Nbs1-deficient lenses developed cataracts at an early age due to altered lens fiber cell differentiation, including disruption of normal lens epithelial and fiber cell architecture and incomplete denucleation of fiber cells. This study demonstrates the importance of MRN function for proper differentiation of the lens fibers cells, suggesting that the same might be true for many other tissues. To further analyze the role of the DDR in CNS development, we recently monitored

the white matter development in Nbs1-CNS-del mice [313]. MRI analysis revealed significant impairment in the organization and levels of the white matter, with minor changes, if any, in gray matter. Biochemical analysis indicated defects in myelin formation and oligodendrocyte development. Furthermore, MRI and functional analyses showed that Nbs1 disruption also led to severe impairment in the development of the eye and optic nerve with severe dysfunction of the photoreceptors (A. Solomon et al., submitted). Of note, the levels of the axonal guidance molecules semaphorin-3A and its receptor neuropilin-1 were up-regulated in the retina of the mutant mice, conditions that resemble brain injury. Collectively, these studies indicate that neuronal tissue organization is dependent on proper DDR function, and inactivation of a key DDR component can lead to severe disruption of the organization of neuronal circuits. Thus, despite the physiological differences between mice and humans, these mouse models have been very useful for demonstrating the intimate connection between proper DDR and CNS development and function [87].

3. The DDR in human aging, and in acute and chronic neurodegenerative pathologies

Compelling evidence points to the central role of accumulating DNA damage in the aging process of CNS neurons and in various neurodegenerative disorders [1,3,4,5,84,123,124,126,127]. However, the aging process does not affect the CNS uniformly [128], and brain regions and types of neurons differ substantially in the amount of DNA damage they accumulate during aging [129]. More DNA damage was found in the aging hippocampus than in the aging cerebellum [130].

An unknown correlation exists between DNA damage, DNA repair and neuron loss in the aging brain: certain types of neurons (such as hippocampal, pyramidal and granule cells as well as cerebellar granule cells) suffer from an age-related accumulation of DNA damage but are not reduced in number during aging. Other types of neurons (such as cerebellar Purkinje cells) are reduced in number during aging, but remaining cells show no age-related accumulation of DNA damage [127]. It was speculated that there is a certain threshold for DNA damage and the cells that exceed this threshold are eliminated. It has also been suggested that neuronal dysfunction during aging is connected mainly to an accumulation of damaged DNA within certain specific types of neurons that do not have an appropriate cell death mechanism for excessive damage [129]. During aging DNA damage was found to be markedly increased in the promoters of important genes, with reduced expression in the aged brain cortex. Moreover, these gene promoters are selectively damaged by oxidative stress in cultured human neurons and show reduced base-excision DNA repair. It has been suggested that accelerated DNA damage may contribute to reduced gene expression in the human brain after age 40, and therefore measures to protect the genome early in adult life may influence the rate of subsequent functional decline and the vulnerability of the brain to age-related neurodegenerative diseases [131].

3.1. *Human late onset neurodegenerative diseases*

Neurodegenerative disorders can be classified based on many criteria, including age of onset, genetic basis, disease characteristics and clinical course, and affected cell types. Typical late onset, chronic diseases (Table 2 and Fig. 1) are Alzheimer's disease (AD) and Parkinson's disease (PD), while monogenic disorders such as the genomic instability syndromes are characterized by early onset and acute manifestation. There are common denominators between these two groups of diseases, and accumulation of DNA damage is one of them [3,5,127,129,132–134]. All of these disorders impair "brain functionality" to various degrees, defined by total input and output of the brain's neuronal circuits. Neurodegenerative disorders deregulate the activity of specific circuits, affecting their organization, cell numbers, cellular functionality, and interactions between cells and circuits. It is reasonable to assume that DDR components that affect early onset neurodegenerative diseases can also be involved in late onset neurodegenerative diseases such as PD or AD.

PD is characterized by profound loss of dopaminergic neurons in the substatia nigra pars compacta. A link between ATM deficiency and dopaminergic cell loss was noted by Eilam et al. [135], who showed that Atm-deficient mice exhibited severe

Table 2 – The DDR in human aging and in multifactorial, late onset neurodegenerative diseases

Syndrome	Affected brain areas	Neurological symptoms	Alterations in DDR pathways and processes	References
Parkinson's disease (PD)	Substantia nigra pars compacta	Dopaminergic cell loss; tremor; bardykinesia; postural rigidity and instability	Increased oxidative stress and DNA damage; activation of mitochondrial BER	[3,303]
Alzheimer's disease (AD)	Cerebral cortex	Progressive neurodegeneration and dementia; memory loss and cognitive decline	Increased oxidative stress; accumulation of oxidative damage; reduced NHEJ; accumulation of DSBs and SSBs; reduction in MRN complex components; activation of cell cycle program	[83,87,127,129,188,165, 233,236,304–310]
Lewy body disease (PSP)	Midbrain	Dementia	Accumulation of DSBs	[311,312]

degeneration of tyrosine hydroxylase-positive, dopaminergic nigro-striatal neurons, and their terminals in the striatum and the ventral tegmental area. Atm-deficient mice were reported to show locomotor abnormalities manifested as stride-length asymmetry, which could be corrected by peripheral application of the dopaminergic precursor L-dopa [135]. In addition, Atm−/− mice were hypersensitive to the dopamine-releasing drug D-amphetamine. This work also showed that dopaminergic neurons are formed normally in the Atm−/− mice, but degenerate during the first few months of life. The data thus indicate that Atm−/− mice exhibit a progressive, age-dependent reduction in dopaminergic cells of the substantia nigra, followed by a reduction in projection neurons of the striatum. Another common denominator between PD and A-T is elevated oxidative stress and oxidative DNA damage. Elevated labile iron in the substantia nigra pars compacta plays an important role in producing reactive oxygen species (ROS), mainly hydroxyl radicals, which subsequently damage nigro-striatal neurons. Interestingly, the iron chelator desferal increased the radioresistance of ATM-deficient cells but did not affect wild-type cells [136], leading the hypothesis that ATM plays a role in cellular resistance to the toxic effects of labile iron. Collectively, these findings may explain the impression that A-T patients show "Parkinsonian" features [137].

4. Oxidative stress, DNA damage and neurodegeneration

Cells possess a wide array of protection mechanisms against ROS, including small reducing molecules, antioxidative enzymes, and damage-repair systems [4,5,7,138,139]. The nervous system has a large oxidative capacity due to a high level of tissue oxygen consumption, but the ability of the brain to withstand oxidative stress is limited [4,5,140]. Chronic exposure to oxidative radicals can adversely affect gene expression and basic metabolic processes [141]. Increasing evidence suggests that oxidative stress is associated with normal aging, neurodegenerative diseases such as AD, PD, Huntington's disease (HD) and ALS [4,5] (see also Schmitz, and Yang et al., in this volume), and genomic instability syndromes [143–147]. Elevated ROS levels and changes in the activities of ROS detoxifying enzymes have been reported in cells derived from patients with xeroderma pigmentosum, Bloom's syndrome, Fanconi anemia and Cockayne syndrome [147,148]. Increased oxidative nuclear and mitochondrial DNA damage have been reported in AD [149] and other neurodegenerative pathologies [4]. The total antioxidant plasmatic status of AD patients was reported to be lower than controls [150]. Together with increased oxidative DNA damage in the aging brain and neurodegenerative pathologies, a reduction in base excision repair – an important repair pathway for oxidative damage – was reported [4,151–153]. Furthermore, reduction in DNA repair capacity after ischemia and reperfusion of nervous tissue may contribute to increased DNA damage and subsequent degenerative effect [154]. Mitochondria are the primary sites of free radical production and their DNA and protein may be more easily damaged [140,149,155]. Today it is clear that the mitochondrial DNA damage response plays a role in aging and neurodegenerative diseases [4,6] (see Yang et al, this volume, for discussion of mitochondrial DNA damage and neuroligical dysfunction).

Environmental factors are known to play a role in the development and chronicity of neurodegenerative disorders, and have led to studies on the contribution of exogenous ROS generators on neurodegenerative processes [156]. Notably, neurotoxicity leading to neurocognitive dysfunction, commonly called "chemobrain", and peripheral neuropathy are among the side effects of cancer treatments based on DNA damaging agents [3,158,159]. Such side effects can often be dose-limiting for chemotherapy [3,160,161].

The causal relationships between deficient DDR and increased oxidative stress have been studied in some detail in the genomic instability syndrome ataxia-telangiectasia (A-T). For further details see Biton et al., in this volume.

5. DNA repair in neurons

If accumulation of lesions in genomic and mitochondrial DNA is an important contributor to neurodegeneration, it is reasonable to assume that neurons will have devised stringent and efficient DNA repair mechanisms. All eukaryotic DNA repair systems operate in neurons, same as in proliferating cells: nucleotide excision repair (NER), base excision repair (BER), mismatch repair (MMR), and the NHEJ and HR pathways of DSB repair. Evidence of BER, NER and MMR activities in neurons is more extensive than the documentation of DSB repair in these cells [3,4,81,87] (see also Souza-Pinto et al., Yang et al., and Nouspikel, this volume). It is assumed that most of the lesions inflicted in neuronal genomic and mitochondrial DNA by ROS, the principal damaging agent in these cells, are repaired via the BER pathway, and this activity has been documented in the nuclear and mitochondrial compartments [3,4,6,81]. DNA repair activity in adult brain has been demonstrated mainly *in vitro* using brain extracts [162–165]. Although DNA repair activity exists in neurons, it was found that DNA lesions are actually repaired more slowly in neurons relative to dividing cells, suggesting that lesions are likely to accumulate [93,162,166–168]. Indeed, following cellular differentiation, there is actually a reduction in the level of many repair components [166,167,169,170]. Global genomic repair (GGR) is attenuated in neurons while the repair of transcribed genes is more vigorous [167]. It is noteworthy, though, that repair efficiency of different lesions varies among different types of neurons [6].

It has been suggested that since terminally differentiated cells do not replicate their DNA, removal of DNA damage from the nonessential bulk of their genome is dispensable, and these cells can afford to repair only the portion of the genome needed for their functions, e.g., their transcribed DNA [166,171]. As the repair process carries a high energy cost, it is reasonable that these active cells will dispense with mechanisms such as GGR. On the other hand, harming the fidelity of information transcribed from genes to proteins could conceivably lead to the formation of defective proteins, or affect the regulation of genes essential for normal neuron functioning, leading eventually to neurodegeneration [3,131]. Interestingly, the repair of the non-transcribed strand is also proficient, a phenomenon termed differentiation-associated repair (DAR),

and later renamed transcription domains-associated repair [171]. Transcription domains-associated repair is probably necessary to maintain the integrity of the template strand needed by transcription coupled repair (TCR) to complete the repair of the transcribed strand with high fidelity [166,171] (see Nouspikel et al., in this volume, for further discussion of DAR). Other repair pathways might exist in higher intensity in neurons due to their unique nature. Several repair genes were indeed found to be up-regulated during neuronal differentiation, among them the XPG and XPF/ERCC1 excision repair proteins [167], and aprataxin (APTX) [172–174] (see also Lavin et al., this volume). Indeed, certain DNA lesions might be more predominant in neurons because of their high oxidative stress [5,138], requiring higher levels and efficiency of the corresponding repair proteins.

Reduction in cellular levels of several DNA damage response proteins, including DNA repair proteins [93,164,166,174–179], does not detract, however, from their critical importance in neurons. While rapid repair might not be critical for their immediate survival, their repair capacity must be sufficient to last the lifetime of the organism [93]. Thus, further reduction in DNA repair proteins has been associated with various neurodegenerative pathologies, as described above.

Just like GGR is attenuated, the HR pathway of DSB repair might also not be an essential repair pathway in mature neurons because of their post-mitotic nature [116]. However, it was recently shown that induction of DNA damage in neurons was followed by a transient increased expression of both HR and NHEJ proteins that correlated with increased DNA repair activity [180]. Induction of components of HR might occur as part of cell cycle re-entry attempts in stressed neurons (see below).

6. The ATM-mediated DDR in neurons

The important observation of McKinnon and co-workers of Atm's pro-apoptotic function in the developing mouse CNS [113,115] has been mentioned above. This work suggested that Atm may function at some developmental survival checkpoint that serves to eliminate neurons with excessive DNA damage. ATM functions have been investigated mainly in cultured proliferating cells, in which its role as the chief mobilizer of the DSB response has been elucidated [11,20,54,181]. However, despite the documented importance of maintaining genomic stability in neurons, the central role of the cell cycle checkpoints in the ATM-mediated DDR posed certain conceptual difficulties in ascribing to ATM in neurons the same function it has in proliferating cells. Furthermore, several investigators suggested that ATM was cytoplasmic in human and murine neuronal tissues and hence was functioning in pathways unrelated to the DNA damage response [177,182,183]. Work in our laboratories showed, however, that in human neuron-like cells and murine cerebellar neurons, ATM is largely nuclear and mediates the DSB response similarly to how it operates in proliferating cells [174,184]. Further support for these findings was published recently by Brooks and co-workers [185]. For further discussion of the ATM-mediated DDR in neurons and its relationship to the A-T phenotype see contributions by O'Driscoll and Jeggo, Biton et al., Frappart and McKinon, and Lavin et al., in this volume.

7. Attempts to re-enter the cell cycle in stressed neuronal cells: are they functional?

Attempts of post-mitotic neurons to re-enter the cell cycle following genotoxic stress have been extensively documented and usually linked to ensuing cell death [186–188]. Importantly, cell cycle re-entry does not accompany neuronal cell death caused by apoptosis inducers that do not cause DNA damage [187,189]. Early studies showed that over-expression of the SV40 large T antigen (Tag) in Purkinje and retinal neurons induced DNA synthesis and cell death, but not cell proliferation or tumorigenesis [186,190,191]. Targeted disruption of the retinoblastoma protein, pRb, also resulted in DNA synthesis and apoptosis of post-mitotic neurons [186,192]. The main mechanism of Rb action is considered to be its interaction with and inactivation of the transcription factor E2F. Crossing E2F-1 trangenic mice with Tag transgenic mice resulted in accelerated Tag-induced ataxia and loss of Purkinje cells, suggesting that E2F-1 contributes to the process of degeneration [190]. These mice models spawned the hypothesis that neuronal cell death results from the abortive attempts of neurons to enter the cell cycle [193]. The rarity of brain tumors and the resistance of neurons to oncogenic transformation are consistent with this idea [191].

7.1. *Cell cycle activation and neuronal death*

There is growing evidence that attempts at cell cycle reactivation are a common feature of apoptosis in post-mitotic neurons during development and disease [186]. Activation of cell cycle mechanisms contributing to neuronal cell death was documented in a wide variety of circumstances [186], including following DNA damage [186,187,189,194–197], and in a variety of human and mouse neurodegenerative diseases including A-T [186,198–209]. It was suggested that once cell cycle reactivation is induced by an insult in post-mitotic cells, the cell's progression through the cycle is dependent on the type of insult and its extent and the type of neuron and its maturity, all of which collectively define a "death threshold" [186,194,210,211]. Kruman et al. [189] suggested that following DSB induction the cell cycle re-entry attempts that are coupled to cell death are ATM-dependent.

The functional link between cell cycle re-entry and cell death were found in many contexts. Cell cycling markers have repeatedly been shown to accompany dopaminergic cell death in the substantia nigra pars compacta in PD. A typical example is high expression of the transcription factor E2F-1 in the affected tissues [212]. Exposure of mice or mesencephalic neuronal cultures to the dopaminergic cell neurotoxins MPTP or MPP^+ resulted in the activation of the retinoblastoma-E2F pathway in post-mitotic neurons prior to their subsequent death. Remarkably, E2F-1 deficient mice were significantly more resistant to MPTP-induced dopaminergic cell death than their wild type littermates. Exposure of cerebellar granule neurons to MPP^+ resulted in increased expression of cyclin D, cyclin E, CDK2, CDK4 and E2F-1. Broad inhibition of CDKs

attenuated the neurotoxic effects of MPP^+ [213]. Work from our lab has shown that exposure of chick sympathetic neurons to dopamine resulted in apoptotic cell death which was associated with fluctuation in the expression of cyclin B2 and PCNA [214,215]. In addition to cerebellar granule neurons, which are sensitive to dopaminergic neurotoxins, Purkinje cells are vulnerable to a variety of insults during development and maturity. Apoptotic death in Purkinje cells had been shown to be associated with markers of active cell cycle and new DNA synthesis in the *staggerer* and *lurcher* mutant mice [216].

An important model demonstrating a link between oxidative damage, cell cycle re-entry and cell death is the harlequin (*Hq*) mouse [217]. In this mutant a proviral insertion reduces the expression of apoptosis-inducing factor (Aif), a mitochondrial flavoprotein with oxidoreductase and peroxide scavenging activities [218]. Consequently, cerebellar neurons and retinal cells in this mouse show increased ROS-induced DNA damage accompanied by the appearance of S-phase markers, which precedes apoptotic death. In rat cerebellar organotypic cultures, CDK inhibitors extended the life of Purkinje neurons, but their morphology appeared abnormal [219]. CDKs involvement was also found in stroke-induced cell death [220]. In patients with spinal cord injury, which may lead to neuronal loss, cell cycle up-regulation was associated with neuronal and oligodedoglial apoptosis, and treatment with the cell cycle inhibitor flavopiridol reduced cell cycle protein levels and significantly improved functional recovery [221,222].

7.2. *Stressed neurons exit G0 and activate components of the cell cycle machinery*

To enter the cell cycle, quiescent neurons must exit G0 and enter into the G1 phase. Several studies reported expression of G1/S cell cycle regulators in neurodegenerative diseases such as AD [200,205,223], vascular dementia [205], and ALS [206], following spinal cord injury [201], in hypoxia-ischemia [224], and in cultured primary neurons undergoing cell death [225]. Moreover, G1/S cell cycle blockers, inhibitors of CDKs, and expression of mutant, dominant-negative CDK4/6 promote the survival of neurons following DNA damage and growth factor withdrawal [195–197,226,227]. It was reported that cyclin D1 is an essential mediator of neuronal apoptotic death, which is p53-independent, but cyclin D1-induced apoptosis depends on Cdk activation [186,228], indicating that the cell cycle machinery is linked to neuronal cell death. Phosphorylation of pRb and activation of E2F in neurons following an apoptotic stimulus, including DNA damage, have also been documented [186,187,196,225]. The mechanism by which CDKs are activated in stressed neurons remains elusive. It was recently suggested that checkpoint kinase 1 (Chk1) is a potential activator of cell cycle in neuronal death induced by DNA damage. In cortical neurons under non-stressed conditions, the basal activity level of Chk1 is relatively high and has been suggested to contribute to the post-mitotic state of neurons. It was reported that in neurons, Chk1 activity is rapidly down-regulated following DNA damage, with concomitant increase in Cdc25A activity. In proliferating cells, Cdc25A phosphatase dephosphorylates and activates CDK4/6/cyclinD1 complex, and following DNA damage is negatively regulated by phosphorylation mediated among others by Chk1. In neurons, inhibition of Cdc25A blocks neuronal death and reduces cyclinD1-associated kinase activity and pRb phosphorylation. Therefore, it has been suggested that the Chk1/Cdc25A axis participates in the activation of cell cycle-mediated neuronal death [229]. Another important mediator of the G1/S cell cycle checkpoint is p53. Cerebellar granule neurons deficient in p53 are protected against apoptosis induced by DNA strand breaks [186]. Like in proliferating cells, the transcription factors E2F and p53 induce in neurons expression of genes that function in death pathways [186,207].

7.3. *Cell cycle activation in neurons and DNA synthesis*

It is debated whether neurons re-entering the cell cycle need to go through DNA synthesis in order to die. Expression of S-phase markers was reported in post-mitotic neurons following DNA damage [189], hypoxia-ischemia [224], and in neurons ectopically expressing E2F1 [230]. In the *Hq* mice mentioned above S-phase markers appear in cells destined to undergo apoptosis following oxidative damage [217]. DNA synthesis was documented in neurons in AD [231], and lately in A-T [209]. FACS analysis showed an increase in S-phase cells among neurons exposed to genotoxic insults [189]. Interestingly, ATM suppression was found to attenuate the damage-induced S-phase re-entry, and consequently the apoptotic process, in damaged neurons [189]. These findings are in line with earlier findings of resistance of neuronal tissues in Atm−/− mice to DNA damage-induced apoptosis [111–113].

Whether or not apoptotic neuronal cells pass the G1/S phase checkpoint and synthesize DNA might be linked to how long cells destined for apoptosis survive after the initial injury [224]. The “death threshold” mentioned above is important in determining the involvement of cell cycle signaling in neuronal death [211]. It was suggested that DNA synthesis itself is a potential source of replication errors. Because differentiated neurons predominantly express DNA polymerase β with high error rate, *de novo* synthesis following neuronal cell cycle re-entry might produce additional DNA damage that eventually leads to cell death [211].

Can these attempts to re-enter the cell cycle go as far as the G2 phase? Expression of G2/M checkpoint markers has been reported in A-T cells [209], AD [223,231], vascular dementia [205], and several other neurodegenerative diseases [202]. CDK1 has been shown to phosphorylate the pro-apoptotic protein BAD in neurons, once again linking cell cycle to cell death machinery [186,232]. It has also been suggested that activation of CDK1 in neurons leads to hyperphosphorylation of other proteins implicated in the pathology of neurodegenerative diseases [202,208].

Despite the data on neuronal cell cycle re-entry through G1/S, DNA synthesis and G2, there is no evidence of entry of neurons into the M phase [186,200,231]. It was previously suggested that the cell death of post-mitotic neurons rather than entry into mitosis and completion of the cell cycle might be due to induction of cell death activators by CDK1, as mentioned above, or the inability of neurons to undergo chromosome segregation and cytokinesis [186]. Another theory is that mitochondrial mass and the concomitant potential to

generate oxygen radicals is highest just before the M phase, increasing oxidative threat and adding further damage to the DNA that leads ultimately to cell death and not mitosis [205].

It has been asked why, if cell cycle proteins are expressed in neurons, they fail to follow cell cycle progression including cell division [223]. The co-expression in the same neurons of cell cycle proteins that normally function in different stages of the cell cycle argues for neurons not completing the cell cycle stages in an orderly manner [200,223]. Also, inhibitory proteins associated with cell cycle exit, such as members of the INK4 family of CDKIs, are up-regulated in vulnerable AD neurons [198,199,223]. Moreover, many of the cell cycle proteins are often found in the cytoplasm in neurons, and not in the nucleus where they would exert their cell cycle-related activities [186,200,202,206,207,223]. This altered localization has led to the speculation that cell cycle proteins carry out functions, other than in cell cycle progression, that contribute to cell death [186,207]. Importantly, there is growing recognition that programmed cell death can be executed not only via the classical, well documented apoptotic programs but also by other, recently elucidated mechanisms [75]. Revisiting the question of how neurons die following genotoxic stress and possible redefinition of this process may shed light on the link between cell cycle re-entry and cell death in these cells.

Rather than cell death, an alternative function of cell cycle re-entry of damaged neurons could be associated with cellular survival pathways. In cycling cells, cell cycle progression following DNA damage is arrested at specific checkpoints to allow time for damage assessment and processing. The cell cycle re-entry of damaged neurons may be required for activation of the repair process. It is noteworthy that various repair enzymes have greater activity in proliferating cells than in post-mitotic neurons, and some of the DNA repair processes are completely attenuated in neurons, as mentioned above. Since lesions are repaired more slowly in neurons than in dividing cells [93,166,167], the triggering of cell cycle re-entry following DNA damage might lead to activation of the DNA repair process by mimicking cycling state [187]. Transient expression of components of the HR repair pathway was reported following apoptotic stimuli, correlated with increased DNA repair [180]. Expression of the base excision repair enzyme Ref-1 was significantly increased in AD compared to controls [233]. DNA-polymerase β, which functions in DNA repair [151–153], is loaded into replication forks in neurons challenged with β amyloid [234]. GADD45a and GADD34 (members of the growth arrest and DNA damage gene family), which are also known to mediate DNA repair together with PCNA, were expressed in post-mitotic neurons following spinal cord injury and focal cerebral ischemia, together with other cell cycle-related genes [201,203]. Thus, it might be that activation of the cell cycle in post-mitotic neurons is intended to activate efficient rapid repair machinery, as in proliferating cells. There might be a threshold over which the pathway to repair DNA damage is no longer active and a death signaling cascade is initiated instead [180,235]. The fact that there is a reduction in DNA repair proteins in neurodegenerative diseases [165,233,236] could make the aborted attempt at cell cycle activation a requirement for efficient repair [233]. While it is still not known whether cell cycle activation is the cause or consequence of the DNA repair and/or neuronal cell death, the mounting data indicate that this process is an essential component of the genotoxic response in neurons.

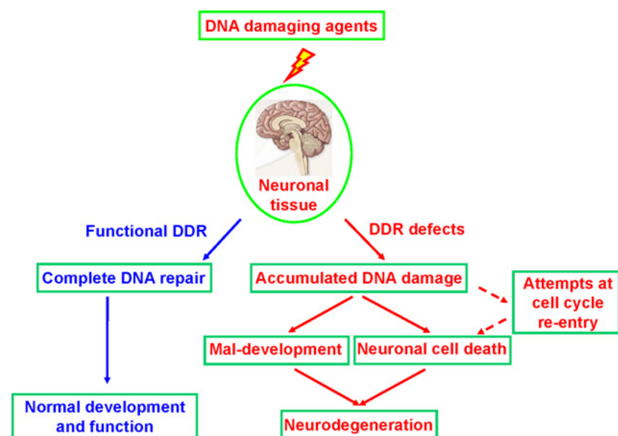

Fig. 2 – Effects of defective DDR pathways on the CNS.

8. Future perspective

Neurons are characterized by elaborate structure and function, perhaps more than any other cell type. The combination of their critical function, post-mitotic nature, finite number and high metabolism demands a robust DNA damage response (Fig. 2). Compelling evidence points to similarities in the DNA damage responses of proliferating and post-mitotic neurons, but the unique nature of neurons requires adaptation of this response to the special cellular environment. Further investigation of the DDR in human genomic instability syndromes and neurodegenerative pathologies, and in animal models of these conditions, is likely to disclose these special features. A cardinal, emerging question is how DNA-damaged neurons die. As the repertoire of programmed cell death forms is expanding [75,237], this question is likely to be revisited. Clarification of the mechanisms at work will help guide the search for novel treatment modalities for a variety of neurodegenerative conditions.

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